

**Behavioral Apathy and Its Relationship with Physical Activity, Affective Attitudes,
and Motor Cortex Excitability**

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Abstract

Apathy is a multidimensional syndrome characterized by diminished motivation and reduced goal-directed behavior. Although apathy is commonly studied in neurological and psychiatric populations, it is also observed in otherwise healthy adults and may represent an important barrier to engagement in physical activity. Because physical activity requires effort, action initiation, and persistence, individuals with higher levels of behavioral apathy may be less likely to initiate and maintain active behavior. Despite growing interest in the relationship between apathy and physical activity, the behavioral and neurophysiological mechanisms underlying this association remain poorly understood. This thesis examined the relationship between behavioral apathy, physical activity, affective attitudes toward physical activity, and motor cortex neurophysiology.

Across four complementary studies, behavioral and neurophysiological pathways that may contribute to reduced physical activity in individuals with higher apathy were investigated. Study 1 is a systematic review and meta-analysis examining the association between apathy and physical activity across clinical and non-clinical populations. Study 2 examined whether intentions, explicit affective attitudes, and approach-avoidance tendencies toward physical activity mediated the relationship between behavioral apathy and physical activity in healthy adults. Study 3 is a systematic review and meta-analysis investigating the association between habitual physical activity and measures of motor cortex neurophysiology, including corticospinal excitability, intracortical inhibition, and intracortical facilitation. Study 4 used transcranial magnetic stimulation (TMS) to examine whether behavioral apathy was associated with these neurophysiological measures in healthy adults. Across the four studies, results demonstrated that apathy is associated with physical activity, but that this association is more strongly explained by motivational and affective processes than by resting-state motor cortex neurophysiology. The

systematic review and meta-analysis showed a significant negative association between apathy and physical activity, with stronger associations in older adults and individuals with Parkinson's disease. Behavioral analyses further demonstrated that higher behavioral apathy was associated with lower physical activity, partly through weaker intentions to be physically active and less positive affective attitudes toward physical activity. Individuals with lower apathy also showed stronger tendencies to approach physical activity stimuli and avoid sedentary stimuli, although these tendencies did not mediate physical activity behavior. In contrast, the neurophysiological studies showed no reliable associations between habitual physical activity and measures of corticospinal excitability, intracortical inhibition, or facilitation. Similarly, behavioral apathy showed negligible associations with these measures, with equivalence testing indicating that any potential effects were too small to be practically meaningful. These results suggest that the relationship between apathy and physical activity is primarily linked to motivational and affective mechanisms rather than stable differences in primary motor cortex neurophysiology. Specifically, higher behavioral apathy was associated with weaker intentions to be physically active and less positive affective attitudes toward physical activity, whereas neither habitual physical activity nor behavioral apathy showed meaningful associations with resting TMS-derived measures of corticospinal excitability or intracortical circuitry. Overall, this thesis refines the understanding of how apathy contributes to physical inactivity and highlights the importance of targeting motivational processes when designing interventions aimed at increasing physical activity engagement.

Keywords: Behavioral Apathy; Physical Activity; Affective Attitudes; Intentions; Transcranial Magnetic Stimulation; Corticospinal Excitability; Intracortical Inhibition; Intracortical Facilitation; Motor Cortex Neurophysiology.

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To my beloved wife, Samaneh

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I would dedicate this thesis to those people who struggle to be physically active.

Chapter 1

General Introduction

1.1. Apathy

What motivates some individuals to pursue their goals, while others appear indifferent, showing little enthusiasm for purposeful behavior? Why do some individuals invest more effort than others in achieving similar rewards? These questions are important as the absence of motivation has substantial societal and personal consequences, impacting educational and employment performance, as well as civic participation (Vansteenkiste et al., 2005). Motivation is a psychological feature that prompts an individual to act toward a desired goal (Mogenson et al., 1980; Arango et al., 2018), both initiating and sustaining goal-directed behaviors (Arango et al., 2018). In healthy individuals, motivation serves as an inner drive fueled by physical needs, such as hunger and thirst, as well as by responses to pleasurable or aversive stimuli (Arango et al., 2018; Mogenson et al., 1980). Apathy, a term used for diminished motivation, was conceptualized as a behavioral disorder of motivation describing individuals whose lack of motivation is not due to decreased consciousness or intellectual deficits (Marin, 1990; Marin, 1991).

The term “apathy” finds its roots in the Greek word “pathos,” meaning passions (Marin, 1990; Stanton et al., 2016). In English language dictionaries, “apathy” is generally described as a lack of interest or motivation (Marin, 1990). Clinically, apathy has been described (e.g., by patients and families) as “the get up and go that got up and went,” or “the spark is missing” with activities that “don’t seem worth it,” or patients stating that they “just don’t know” why they no longer engage in behaviors they used to do (Le Heron et al., 2018). The concept of apathy as a clinical syndrome emerged from early case studies of brain lesions, describing patients with relatively intact cognitive function who showed a notable lack of observable spontaneous active behaviors, but who were still capable of reacting and behaving almost normally in response to external stimulation (Cairns et al., 1941).

In the early 1990s, apathy began to be considered a syndrome rather than a mere symptom of another condition, and was defined as a state of primary motivational impairment characterized by reduced goal-directed behaviors (e.g., lack of productivity, effort, initiative, and perseverance), reduced goal-directed cognitions (e.g., lack of interest in learning new things, in new experiences, lack of concern about one's personal and health problems, reduced socialization), and reduced emotional concomitances of behavior (e.g., flat affect, emotional indifference) (Marin, 1990; Marin, 1991). To date, the dominant theoretical frameworks still consider three subtypes of apathy: behavioral, cognitive, and emotional (Robert et al., 2009; Costello et al., 2024), with a fourth subtype, social apathy, recently proposed but requiring further research (Dickson et al., 2022).

Levy and Dubois (2006) proposed that behavioral apathy stem from difficulties in elaborating the plan of actions necessary for behavior. Individuals exhibiting behavioral apathy demonstrate the most severe form of apathy, characterized by struggle in self-initiating actions or thoughts, often described as a sense of “mental emptiness.” It seems that inability to reach the threshold of initiation/activation of thoughts or actions when person should behave on an internal motivation contributes to this apathy. This syndrome can be assessed, in apathy scales, by questions contrasting self- and externally-driven behaviors in activities of daily living such as “Does someone have to tell you what to do each day?” and “Do you need a push to get started on things?”

Cognitive apathy refers to inability to self-activate thoughts or self-initiate actions (Levy & Dubois, 2006). It arises from deficiencies in several executive functions required to plan and execute the goal-directed behaviors, including impairments in planning, working memory, rule-setting, and set-shifting. Consequently, patients may exhibit apathy due to deficits in working memory and planning (sustaining and mentally manipulating goals and subgoals), difficulty in

generating new rules or strategies, or difficulty in shifting from one mental and behavioral set to another.

Emotional apathy is the incapacity to establish the connections between emotional signals and behavior (Levy & Dubois, 2006). Emotions and affect are thought to be involved in interpreting the context of behavior and in providing its motivational value (Levy & Dubois, 2006). Any disruption in the connection between emotion-affect and behavior can result in apathy, either by diminishing the willingness to perform actions (loss of will, loss of goals, emotional blunting) and sustain them to completion or by impairing one's ability to evaluate the consequences of future actions. Apathy related to a disruption of "emotional-affective" processing may typically be assessed in apathy scales by questions such as "Does anything interest you?", "Are you concerned about your condition?", and "Are you interested in learning new things?"

1.2. Prevalence of Apathy

Apathy has been recognized across various neurodegenerative diseases (Levy & Dubois, 2006; Lanctôt et al., 2017; Yan et al., 2023) and is considered an independent risk factor for other diseases (Eurelings et al., 2014). Notably, apathy is prevalent in a spectrum of neurological and psychiatric disorders (Fahed et al., 2021), extending its presence even to individuals without underlying health conditions (Pardini et al., 2016; Hwang et al., 2004; Onyike et al., 2007; Geda et al., 2008; Lyketsos et al., 2000; Groeneweg-Koolhoven et al., 2014).

Although prevalence estimates vary widely depending on assessment tools and the clinical population studied, apathy is associated with a broad range of brain disorders (Table 1-1). Several neurodegenerative, vascular, inflammatory, infectious, and traumatic brain pathologies have been associated with the development of apathy, while it is also a component of the negative symptoms of schizophrenia and major depressive disorder. Apathy can be the first clinical marker of a

developing condition (Johansson et al., 2020), as in Parkinson's disease (Pagonabarraga et al., 2015), and in some other conditions (e.g., Huntington's disease), apathy has been shown to closely track disease progression (Naarding et al., 2009). Apathy can also be an early sign of cognitive decline and can be considered "a marker of the severity and evolution of mild cognitive impairments" (Onyike et al., 2007; Geda et al., 2008). Apathy is also a common and disabling feature of frontotemporal dementia and is the part of diagnostic criteria for behavioral variant of this dementia (Rascovsky et al., 2011).

As shown in Table 1-1, some of the most alarming rates of apathy have been reported in patients with progressive supranuclear palsy (>58%) (Flavel et al., 2022) and frontotemporal dementia (>50%) (Parrotta et al., 2024). Apathy is prevalent across various brain disorders, with cortical conditions showing a prevalence of around 50-60% and subcortical conditions around 30-40% (Van Reekum et al., 2005). Additionally, apathy is not limited to brain disorders but also manifests in healthy young adults (1.5%) (Pardini et al., 2016) and older adults with unimpaired cognitive function (2-7%) (Hwang et al., 2004; Onyike et al., 2007; Geda et al., 2008; Lyketsos et al., 2000; Groeneweg-Koolhoven et al., 2014). A longitudinal study tracking apathy in normal aging indicates a gradual increase over a five-year period, particularly among males and individuals over 65 (Brodaty et al., 2010). Furthermore, using the apathy subscale of the Geriatric Depression Scale (GDS-3), Grool and collaborators (2014) discovered that 49% of healthy individuals over 77 years old were affected by apathy, underscoring a significant public health concern. Recent evidence further shows that even in young healthy populations, 29% exceed subclinical (trait-level) cut-offs for apathy and 9% exceed clinical cut-offs (Lafond-Brina et al., 2022).

Table 1-1. Prevalence of apathy in non-healthy and healthy populations

CONDITION	PREVALENCE	COMMENTS
Parkinson Disease (den Brok et al., 2015)	40%	Apathy is a common non-motor symptom of Parkinson Disease
Alzheimer Disease (Leung et al., 2021)	50%	Apathy in Alzheimer Disease likely has the greatest level of research interest
Frontotemporal Dementia (Parrotta et al., 2024)	54%	A core feature of behavioral variant Frontotemporal Dementia
Stroke (Zhang et al., 2023)	33%	There is a slightly higher rate of apathy in right-hemisphere stroke (31.8%) than in stroke involving the left hemisphere (22.2%).
Traumatic Brain Injury (Al-Adawi et al., 2004; Kant et al., 1998)	20-72%	Rate of apathy in Traumatic Brain Injury is very similar to that found in Alzheimer Disease, suggesting that different brain pathologies, which involve the cortex, may cause apathy at similar rates
Schizophrenia (Mulin et al., 2011, Yazbek et al., 2014; Faerden et al., 2010)	47-53%	One of the core negative symptoms of schizophrenia
Progressive Supranuclear Palsy (Flavel et al., 2022)	>58%	It has the highest rate of apathy, that is, occur in nearly all patients with PSP
Mild Cognitive Impairment (Robert et al., 2006)	30%	Apathy in the context of mild cognitive impairment suggests an increased risk of developing AD
Multiple Sclerosis (Novo et al., 2016)	43%	Limited research
Healthy older adults (Hwang et al., 2004; Onyike et al. 2007; Geda et al., 2008; Lyketsos et al., 2000; Groeneweg-Koolhoven et al., 2014)	2-7%	Limited research
Healthy young adults (Pardini et al., 2016)	1-9%	Limited research

1.3. Apathy Is Not Depression

Apathy, often mistaken for depression (Marin, 1990; Kant et al., 2002) because of overlapping symptoms, such as loss of interest, fatigue, and impaired executive functioning, is characterized by reduced motivation and goal-directed behaviors. In contrast, depression is primarily defined by low mood and diminished interest or pleasure in regular activities. Although apathy is often clinically viewed as a symptom of depression, it is increasingly recognized as a distinct syndrome (Green et al., 2022; Ishii et al., 2009). It has therefore been proposed that apathy

reflects either a primary deficit or a secondary manifestation associated with conditions, such as depression (Kant et al., 2002).

Although apathy and depression share certain symptoms, such as diminished interest, psychomotor retardation, fatigue/hypersomnia, and lack of insight, each also presents distinct features. Symptoms more characteristic of apathy include blunted affect, indifference, reduced social engagement, diminished initiation, and poor persistence, whereas symptoms more characteristic of depression include dysphoria, suicidal ideation, self-criticism, feelings of guilt, pessimism, hopelessness, and sleep disturbance (Tagariello et al., 2009). Anhedonia, defined as the loss or reduction of the ability to experience pleasure, serves as a significant distinguishing characteristic between depression and apathy (Husain & Roiser, 2018). It is a major feature of depression, whereas apathy is characterized by a lack of motivation or drive (Marin & Wilkosz, 2005). Consequently, individuals with apathy may not necessarily experience anhedonia, unlike individuals with depression, for whom anhedonia is considered a core symptom (Tagariello et al., 2009). In terms of measurement, depression assessments often include items that align with apathy, potentially leading to an overestimation of depression and an underestimation of apathy (Levy et al., 1998; Lanctôt et al., 2023). Apathy is characterized by specific diagnostic criteria and neuroanatomic substrates, which, although partially overlapping with major depressive disorders, clinically distinguish the two conditions (Lanctôt et al., 2023; Hollocks et al., 2015). When apathy and depression coexist, they may be clinically and anatomically distinct, exhibiting different associations with other signs and symptoms (Green et al., 2022; Lanctôt et al., 2023). For instance, measurements of cortical thickness showed that only apathy severity was correlated with changes in the right frontal and temporo-parietal lobes (Basavaraju et al., 2020). Several procedures have been used to examine the distinction of apathy and depression as independent clinical phenomena

including the evaluation of the rates and association between apathy and depression in different groups, exploring the relationship of apathy and depression with other clinical variables (i.e., stage of disease, cognitive impairment, and functional impairment), the appraisal of their independent associations with cognitive functioning, and examination of the differential effects of treatment on apathy and depression (Green et al., 2022; Lanctôt et al., 2023).

1.4. Brain Mechanisms of Apathy

While the behavioral manifestations of apathy offer valuable insights into individuals' experiences, they are not sufficient to identify the factors correlated with, or predictive of, apathy. To achieve a comprehensive understanding, it is needed to explore the underlying brain mechanisms and identify common neural pathways associated with this condition. By doing so, the root causes of apathy and key influencing factors can be studied, thereby paving the way for addressing apathy more effectively. The brain circuitry thought to mediate motivation include the prefrontal cortex, basal ganglia, and limbic system (Levy & Dubois, 2006). It has become increasingly clear that apathy is a multidimensional syndrome (Levy & Dubois, 2006) and a network disorder (Husain & Roiser, 2018; Bonnelle et al., 2016) rather than the consequence of dysfunction within a single brain region. That is, apathy has been associated with structural and functional alterations within distributed fronto-basal ganglia circuits involved in effort- and reward-based decision-making (Husain & Roiser, 2018 ; Le Heron et al., 2019). These regions include the supplementary motor area (SMA) (Bonnelle et al., 2016), orbitofrontal cortex (Huang et al., 2013), ventral striatum (Mehak et al., 2023), nucleus accumbens (Carriere et al., 2014), which are involved in effort valuation, reward valuation, and the integration of effort and reward information (Croxson et al., 2009; Hogan et al., 2019; Suzuki et al., 2020; Kroemer et al., 2016).

Studies examining the neuroimaging correlates of the apathetic syndrome have identified consistent associations between apathy and disruption of fronto-striatal circuits and in particular anterior cingulate cortex, medial orbitofrontal cortex, and ventral striatum, which includes the nucleus accumbens (Le Heron et al., 2018; Le Heron et al., 2019). These changes are present across a disparate range of underlying pathologies and identifiable using multiple imaging techniques such as functional Magnetic Resonance Imaging (MRI) (Simon et al 2010; Strauss et al., 2014; Fazio et al., 2016) and functional Near-Infrared Spectroscopy (fNIRS) (Talamonti et al., 2022). This suggests a role for these structures to be affected in individuals with apathy. In addition, activity changes related to effort and reward valuation during decision-making have also been observed in the primary motor cortex (M1) (Klein-Flugge et al., 2012; Klein et al., 2012; Derosiere et al., 2017a; Derosiere et al., 2017b), suggesting a functional link between fronto-basal ganglia circuits and M1 that may contribute to effort-based decisions and, potentially, apathy. To interpret how disruption in these regions may give rise to apathy, it is first important to consider a broader framework of how motivated behavior is generated.

1.4.1. Neurocomputational Framework of Motivated Behavior and Apathy

Motivated behavior is characterized by active efforts to attain rewards and is thought to rely on three interacting processes. First, an internal valuation system assesses the subjective value of ongoing events by weighing anticipated benefits against potential costs, such as effort and delay. Second, a motor system interacts with the environment to pursue valued outcomes and avoid aversive events. Third, a mediating system, guided by the valuation system, energizes the motor system toward specific objectives (Le Heron et al., 2018; Le Heron et al., 2019).

The valuation system, comprising the ventral striatum and ventromedial prefrontal cortex, guides behavioral responses, while the ventral striatum and anterior cingulate cortex act as critical

limbic-motor interfaces (Haber et al., 2014). Behavior production is mediated by the motor system, including the posterior mid-cingulate cortex, SMA, and dorsal striatum, influenced by inputs from valuation and mediating systems (Le Heron et al., 2018; Le Heron et al., 2019). Disruption within this fronto-striatal network, including the prefrontal cortex, ventral striatum, anterior cingulate cortex, and motor-related regions, such as the SMA, may impair valuation, effort allocation, or the translation of intention into action, resulting in apathy, a state characterized by diminished drive for self-initiated goal-directed behavior (Levy & Dubois, 2006).

1.4.2. Apathy Across Brain Disorders

1.4.2.1. Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder marked by dopaminergic deficits (Kalia & Lang, 2015). Apathy is common across all stages of Parkinson's disease, may precede motor symptoms, and is associated with reduced quality of life (Aarsland et al., 2009; Le Heron et al., 2018; Le Heron et al., 2019; Pagonabarraga et al., 2015). Using MRI in Parkinson's disease, apathy has been associated with greater atrophy in the nucleus accumbens and caudate, as well as reduced functional connectivity within fronto-striatal circuits, particularly between medial frontal regions and the striatum (Carriere et al., 2014; Baggio et al., 2015).

1.4.2.2. Alzheimer's Disease

Alzheimer's disease is a common dementia in which apathy is highly prevalent and linked to faster cognitive and functional decline (Lane et al., 2018; Lanctôt et al., 2017; Lanctôt et al., 2023; Mehak et al., 2023; Fan et al., 2021). Recent studies suggest that apathy in Alzheimer's disease is associated with reduced metabolism and structural and functional alterations in frontal regions, particularly the orbitofrontal and anterior cingulate cortices, as well as subcortical regions

such as the ventral striatum and medial thalamus (Holthoff et al., 2005; Rosen et al., 2005; Mehak et al., 2023).

1.4.2.3. Frontotemporal Dementia and Progressive Supranuclear Palsy

Apathy is a core feature of frontotemporal dementia, an early-onset dementia (Ratnavalli et al., 2002), and progressive supranuclear palsy (Coughlin et al., 2020; Malpetti et al., 2021; Flavell et al., 2022). In both conditions, apathy is associated with poorer prognosis, and loss of functional independence (Malpetti et al., 2021; Flavell et al., 2022), and has been linked to structural changes in frontal and subcortical regions including the anterior cingulate cortex and orbitofrontal cortex, as well as white matter damage in progressive supranuclear palsy (Rosen et al., 2005; Agosta et al., 2014).

1.4.2.4. Stroke

Stroke is an acute focal neurological syndrome caused by vascular injury (Murphy et al., 2020). Apathy is a common early symptom following both ischemic and hemorrhagic stroke and may persist for up to a year (Caeiro et al., 2013; Tay et al., 2021). Apathy has been linked to lesions in the basal ganglia and medial frontal regions, particularly the anterior cingulate cortex (Le Heron et al., 2018; Le Heron et al., 2019), as well as reduced functional connectivity within frontal networks (Siegel et al., 2014). In stroke, apathy has been linked to lesions in frontal and subcortical regions, particularly the anterior cingulate cortex and caudate nucleus, as well as disrupted frontal network connectivity (Le Heron et al., 2018; Le Heron et al., 2019; Siegel et al., 2014).

1.4.2.5. Traumatic Brain Injury

Traumatic brain injury is acquired brain damage unrelated to degenerative or congenital conditions (Menon et al., 2010). Apathy is a common consequence and appears largely independent of injury timing or age at onset (Green et al., 2022; Ishii et al., 2009). In traumatic

brain injury, apathy has been associated with reduced volume in frontal regions, particularly the medial frontal cortex (Guild et al., 2015).

1.4.2.6. Common Brain Substrate Across Disorders

Even though different studies have looked at various brain conditions and used different methods to investigate apathy, they all agree on one thing: when it comes to apathy, there is a consistent pattern in what parts of the brain is involved: Medial frontal cortex and subcortical structure. Apathy is associated with disruption of medial frontal cortex and subcortical structures including the ventral striatum, medial thalamus, or connections between these regions (Le Heron et al., 2018; Le Heron et al., 2019). Broadly, apathy is one of the clinical consequences of the disruption of the prefrontal cortex-basal ganglia axis, one of the functional systems involved in the generation and control of self-generated purposeful behavior. Apathy is categorized in three subdomains according to clinical observations. Each of these subdomains can be ascribed to lesions of different prefrontal cortex-basal ganglia territories as follows: Emotional apathy is associated with dysfunctions in the orbital and medial prefrontal cortex and its connected region, the ventral striatum (Levy & Dubois, 2006). Cognitive apathy is associated with impairment in the lateral prefrontal cortex and lesions of the dorsal territories of the basal ganglia, in particular lesions of the dorsal portion of the head of the caudate nucleus leading to disruption of cognitive processing mostly related to difficulties in elaborating new patterns of behavior (Levy & Dubois, 2006). Behavioral apathy is associated with lesions in the basal ganglia, which often impact both cognitive and limbic territories, as well as the dorsal-medial aspect of the prefrontal cortex. Specifically, behavioral apathy may manifest following frontal lesions impacting white matter (Levy & Dubois, 2006). Moreover, observations of apathy following basal ganglia lesions resemble outcomes seen with direct lesions of the dorsal-medial prefrontal cortex. Indeed, a

reduction of spontaneous behaviors is often found after direct lesions of the medial wall of the frontal lobes, including the dorsal-medial prefrontal cortex, the premotor medial frontal cortex and the dorsal part of the anterior cingulate cortex (Levy & Dubois, 2006).

1.4.2.7. Healthy Population

While the quantity of studies exploring the brain mechanisms of apathy in healthy populations remains limited, we aim to provide an overview of research efforts aimed to understanding this phenomenon. Bonnelle et al. (2016) tried to establish a biological basis for behavioral apathy by postulating that behavioral apathy in young healthy adults might be associated with differences in brain systems underlying either motivation to act or in action processing (transformation of an intention into action). Their results demonstrate that behavioral apathy is associated with increased effort sensitivity and greater recruitment of neural systems involved in action anticipation (brain's ability to prepare and plan for an upcoming movement or action before it is executed). This involves predicting the demands of the action, such as the effort required, and mobilizing the necessary neural resources to carry it out. The SMA and cingulate motor cortex are brain regions implicated in this anticipatory phase of movement. They help in planning and initiating movements, ensuring that the body is ready to execute the intended action. In addition, decreased structural and functional connectivity between anterior cingulate cortex and SMA were associated with increased behavioral apathy indicating that alteration in effort sensitivity and translation of intentions into actions within this brain regions might make a critical contribution to behavioral apathy (Bonnelle et al., 2016). Building on these findings, Derosiere et al. (2025) further demonstrated that apathy is associated with alterations in distributed fronto-basal ganglia-motor circuits involved in effort-based decision-making. In a cohort of healthy individuals, higher apathy scores were linked to increased structural connectivity in SMA–M1, SMA–basal

ganglia, and orbito-frontal cortex–basal ganglia pathways, as well as enhanced facilitatory effective connectivity from the orbito-frontal cortex to M1, likely mediated through basal ganglia circuits. Importantly, the study showed that different dimensions of motivated behavior rely on partially distinct neural substrates: Effort sensitivity was primarily associated with SMA-related circuits, whereas reward sensitivity was linked to nucleus accumbens–pallidal pathways and intra-M1 Gamma-Aminobutyric Acid (GABA)-ergic inhibitory circuits. Interestingly, reduced motivational engagement, characterized by higher apathy, increased effort sensitivity, and lower reward sensitivity, was consistently associated with stronger connectivity across several of these circuits. Although this pattern may appear counterintuitive given evidence of reduced connectivity in clinical populations, it aligns with the notion that both hypo- and hyper-connectivity may reflect maladaptive network dynamics. In this context, increased connectivity may represent inefficient processing or a compensatory mechanism in individuals with subclinical apathy. These findings reinforce the view that apathy is not localized to a single brain region but reflects dysfunction within a distributed network integrating valuation and motor processes, while also highlighting the active role of M1 in motivated behavior. In 2016, Fazio and collaborators sought to investigate the impact of apathy on brain processing during cognitive tasks by examining the association between apathy and neural correlates of higher-order cognitive processing in a cohort of healthy young individuals. Their findings indicated that heightened apathy is linked to increased activity in the dorsolateral prefrontal cortex during cognitive tasks (working memory and attentional performance tasks), reflecting an elevated need for prefrontal resources in processing cognitive stimuli. Moreover, elevated apathy levels were associated with reduced functional connectivity between the dorsolateral prefrontal cortex and the basal ganglia during cognitive processes (Fazio et al., 2016). Apathy in older adults reflects disturbances in neural connectivity linked to reward-

and salience-related processing. This is evidenced by the negative association between apathy and functional connectivity of the right insular cortex and right anterior temporal regions, as well as functional connectivity of the left orbitofrontal cortex and anterior cingulate regions (Jang et al., 2021). Moreover, cognitive subtype of apathy was found to be associated with executive deterioration, which can be partially ascribed to decreased functional connectivity between the frontal and ventral striatum (Kawagoe et al., 2017). That underscores the association between cognitive apathy and executive function decline, emphasizing the degradation of functional connectivity between the ventral striatum and frontal region even in healthy aging individuals. Furthermore, apathy symptoms were associated with volume reductions in both grey, particularly in the frontal and temporal lobes (Grool et al., 2014), right anterior cingulate (Lavretsky et al., 2007), and white matter regions (Grool et al., 2014). Notably, white matter lesions are thought to contribute to apathetic behavior (Yao et al., 2015; Grool et al., 2014; Lavretsky et al., 2007) and to subsequently affect different aspects of individuals life.

1.5. Apathy, Cognitive Function, and Physical Activity

Apathy is linked to poorer health outcomes in individuals with neurological disorders, correlating with greater morbidity and mortality in these conditions (Barone et al., 2009; Vilalta-Franch et al., 2013; Lansdall et al., 2019). Individuals often lack insight into apathy, either failing to recognize it or not perceiving it as problematic. Despite the considerable burden it imposes, caregivers may not recognise apathy as an issue, as they may interpret the person's behavior as laziness or view it as an inevitable response to their illness rather than a core aspect of the disease (Brodaty et al., 2010). Apathy affects several domains, including cognition (Kawagoe et al., 2017; Montoya-Murillo et al., 2017) and physical health (Ayers et al., 2017; Henstra et al., 2019b), positioning itself as a crucial behavioral syndrome in clinical settings.

1.5.1. Apathy and Cognitive Function

Regarding cognitive function, apathy is associated with lower cognitive performance in older adults with normal cognitive functioning (Onyike et al., 2007), cognitive decline (mild cognitive impairment) (Geda et al., 2008), transition to dementia (Pink et al., 2015; Guercio et al., 2015), and dementia severity (Mega et al., 1996; Lanctôt et al. 2017). Therefore, apathy could be considered a marker of impending cognitive decline and future risk for dementia (Onyike et al., 2007). The cognitive dysfunction associated with apathy manifests in reduced performance on cognitive tasks, impaired executive function, decreased verbal fluency, diminished attention, and slower information processing speed (Brodaty et al., 2010; Kawagoe et al., 2017).

1.5.2. Behavioral Apathy and Physical Activity

Beyond its cognitive consequences, apathy has also been associated with poorer physical functioning and reduced participation in everyday activities (Ayers et al., 2017; Brodaty et al., 2010). One important pathway through which apathy may influence physical health is physical activity. Physical activity, including exercise, sports, active travel (cycling, walking), household chores, and work-related physical activity (Cheval et al., 2021), is now widely recognized as one of the top contributors to physical and mental health, improving cognitive functioning (Cheval et al., 2023) and reducing rates of cardiovascular disease (Wahid et al., 2016), cancer (Moore et al., 2016), hypertension (Liu et al., 2017), diabetes (Cheval et al., 2021), obesity (Bleich et al., 2018), depression (Boisgontier et al., 2020), and functional dependence (Boisgontier et al., 2020; van Allen et al., 2024). Despite these benefits, over one in four adults fails to meet the recommended levels of physical activity. This lack of physical activity has prompted countries including Canada to make physical activity a priority area (Ministry of Health, 2020). Research indicates that one of

the key barriers to engage in physical activities is apathy (Franco et al., 2015), suggesting that apathy may be an important factor contributing to physical inactivity across populations.

In a study on people with multiple sclerosis, higher physical and leisure activity levels were associated with lower apathy levels (Vanner et al., 2008). Two separate studies (Farholm et al., 2017; Ringen et al., 2018) investigated the link between apathy and physical activity in severe mental illness, confirming a negative correlation. However, in women over seventy with breast cancer, this correlation was not statistically significant (Lemij et al., 2023). People with myotonic dystrophy may experience apathy, but a study found no significant relationship between physical activity and apathy (Knak et al., 2020). Similarly, in both moderate and severe Alzheimer's disease, Ishimaru et al. (2020) found no correlation between apathy and physical activity. In research on Parkinson's disease and stroke, there is a relatively higher number of studies exploring the connection between physical activity and apathy compared to other diseases. In Parkinson's disease research, all studies have reported a significant association between physical activity and apathy. Abrante et al. (2012) found a slight connection between the International Physical Activity Questionnaire (Craig et al., 2003) and the Apathy Evaluation Scale (Marin, 1991). Miura et al. (2014) further explored this, finding a marginal yet meaningful relationship with apathy, particularly noting higher apathy levels in non-engaged-physical activity individuals (Miura et al., 2014). Sacheli et al. (2018) reinforced these findings despite limited participants ($n = 17$), highlighting a moderate correlation ($r = -0.40$). Gorzkowska et al. (2020) revealed a negative relationship between apathy and physical activity in over a hundred participants (Gorzkowska et al., 2020). Ng et al. (2021) observed a significant negative relationship ($r = -0.23$) between apathy and physical activity, even within one year of follow-up. In stroke survivors, apathy may lead to increased sedentary behavior, with significant associations found in several studies (Hamre et al.,

2021; Ito et al., 2020). Ito et al. (2020) observed a correlation between apathy and daily step counts among stroke survivors ($r = -0.32$). Likewise, Hamre et al. (2021) reported a notable negative association between self-reported physical activity and apathy in this population. However, Hüseyinsinoğlu et al. (2017) found no significant link between apathy and physical activity, measured either via self-reported questionnaires or accelerometers (Hüseyinsinoğlu et al., 2017). Furthermore, when apathy was analyzed as a continuous scale, no significant correlation with daily steps was found (Ito et al., 2021).

The relationship between physical activity and apathy in healthy older adults exhibits inconsistency (Table 1-2). Grool et al. (2014) found a significant association between apathy and physical activity, while Yao et al. (2015) and Hashimoto et al. (2016) linked apathy solely with leisure physical activity. Henstra's studies supported this link (Henstra et al., 2018; Henstra et al., 2019a; Henstra et al., 2019b; Henstra et al., 2022). However, Talamonti et al. (2022) found no correlation between apathy and physical activity. Although studies have demonstrated the presence of apathy in young adults, none have examined the correlation between physical activity levels and apathy in this population. Therefore, as argued, while the motivational impairment that defines apathy is likely to reduce the engagement in physical activity, there is discrepancy in the literature. Taken together, these inconsistencies and gaps highlight the need for a comprehensive review to clarify the nature of the relationship between apathy and physical activity. Furthermore, given the limited evidence examining this relationship in healthy adults, particularly the absence of studies in young adults, investigating the association between apathy and physical activity in healthy adults across the adult lifespan is integral.

Table 1-2. Characteristics of studies assessing the relationship between physical activity and apathy in older adults

Study (Year)	N (#women)	Mean age (SD/range)	Health status	Mean apathy (SD or range)	Mean physical activity (SD or range; measure)	Correlation	p-value
Grool (2014)	4354 (2548)	76 (5.4)	Older adults	n.a. (dichotomized; GDS-apathy subscale)	n.a. (ad-hoc questionnaire)	$r = -0.05^{\dagger}$	<0.001
Hashimoto (2016)	213 (114)	68.9 (7.5)	Older adults	n.a. (AS)	n.a. (modified BHPAQ) Leisure (5-point scale) work (5-point scale) sport (< vs. ≥ 4 MET-h/week)	OR = 0.59 n.a. n.a.	<0.05 >0.05 >0.05
Henstra (2018)	243 (161)	75.8 (7.0)	Older adult fallers	n.a. (dichotomized; GDS-apathy subscale)	n.a. (ad-hoc questionnaire)	$r = -0.15^{\dagger}$	0.016
Henstra (2019a)	380 (247)	69 (11)	Healthy and depressed older adults	n.a. (dichotomized; AS)	2231(1989; MET-min/week; IPAQ)	B = -59.8 $r = -0.17^{\dagger}$	<0.001
Henstra (2019b)	2893 (1416)	73.3 (6.6)	Older adults	n.a. (dichotomized; GDS-apathy subscale)	135.4 (80.8; LAPAQ)	$r = -0.06^{\dagger}$	<0.001
Henstra (2022)	394 (278)	69.3 (6.9)	Healthy and depressed older adults	n.a. (AS)	n.a. (IPAQ; low vs. moderate vs. high)	$r = -0.17^{\dagger}$	<0.001
Krell-Roesch (2023)	3222 (1433)	79.2 (65.6)	Healthy and MCI older adults	188 (6; NPI-Apathy subscale)	6.5 (3.9) (NHIS/MHS PAQ)	OR = 0.89 $r = -0.32^{\dagger}$	<0.001
Talamonti (2022)	41 (26)	66.93 (5.3)	Healthy older adults	n.a. (GDS-apathy subscale)	n.a. (dichotomized; ad-hoc questions)	$r = -0.25$	0.67
Yao (2015)	317 (180)	64.5 (10.2)	Healthy older adults	467 (113; AS)	n.a. (modified BHPAQ) Leisure (5-point scales) work (5-point scales) sport (dichotomized; MET-h/week)	$\beta = -0.25$ $\beta = -0.05$ $\beta = -0.09$	<0.001 >0.05 >0.05

AS = Apathy Scale, B = unstandardized regression coefficient, BHPAQ = Baecke questionnaire, Habitual Physical Activity, GDS = Geriatric Depression Scale, IPAQ= International Physical Activity Questionnaire, LAPAQ = LASA Physical Activity Questionnaire, MCI = Mild Cognitive Impairment, NHIS/MHS PAQ = National Health Interview Survey and the Minnesota Heart Survey Physical Activity Questionnaire, NPI = Neuropsychiatric Inventory Questionnaire, OR: Odds Ratio, r = Pearson's correlation coefficient, β = standardized regression coefficient

To date, several studies have explored the association between apathy and physical activity in healthy populations, primarily focusing on the elderly, with diverse outcomes. These studies mostly used unspecified apathy scales (e.g., Geriatric Depression Scale (Grool et al., 2014; Henstra et al., 2018; Henstra et al., 2019b; Talamonti et al., 2022), Neuropsychiatric Inventory (Krell-Roesch et al., 2023)) or general apathy questionnaires (Apathy Scale) (Hashimoto et al., 2016; Yao et al., 2015; Henstra et al., 2022). However, little is known about this relationship in adults across the lifespan, despite evidence that apathy is also present in younger and middle-aged populations. Further investigation using more specific measures of apathy, such as the behavioral apathy subscale of the Lille Apathy Rating Scale (LARS), may help clarify the relationship between apathy and physical activity. The LARS distinguishes between behavioral, emotional, and cognitive apathy, enabling a focused assessment of behavioral apathy (Dickson et al., 2022). Additionally, the LARS is regarded by some experts as the most suitable scale for evaluating apathy in non-institutionalized individuals (Fernández-Matarrubia et al., 2016).

1.5.3. Behavioral Apathy

Behavioral apathy is of particular interest because it reflects reduced motivation to initiate and sustain behavior and directly translates into actions or inactions, making it especially relevant to the study of physical activity and the most relevant subtype of apathy to examine in this context. Studies have shown that levels of brain activation (greater recruitment of neural systems particularly anterior cingulate cortex and SMA) during the decision-making phase are positively correlated with behavioral apathy. This indicates that individuals who are more behaviorally apathetic face a greater brain-energetic cost when making cost–benefit decisions about whether the physical effort required is worth the reward or not (Bonnelle et al., 2016).

The relationship between behavioral apathy and effort anticipation has been well-documented (Bonnelle et al., 2016), that is, people who are more apathetic recruit more neural resource in anticipation of execution of an effortful action, causing them to struggle more with initiating behavior. Conversely, no such relationship has been found in the emotional and cognitive domains of apathy (Bonnelle et al., 2016). Among all subdomains of apathy, behavioral apathy has the highest level of correlation with motor function among different population with chronic condition (van Dorst et al., 2021; Thompson et al., 2023) and showed correlation with everyday activities (Ang et al., 2018), suggesting that behavioral apathy is the most relevant area to assess its relationship with physical activity.

Establishing whether behavioral apathy is associated with physical activity is important, but identifying the potential mechanisms underlying this relationship is equally important. A better understanding of these mechanisms may improve the design and specificity of rehabilitation interventions aimed at addressing physical inactivity in individuals with apathy. However, these mechanisms remain largely overlooked and poorly understood. Given their established links to both motivation and physical activity, processes such as intentions, explicit attitudes, and approach–avoidance tendencies toward physical activity may play an important role in explaining how behavioral apathy relates to physical activity engagement.

1.5.4. Apathy and Attitude Toward Physical Activity

Engagement in physical activity is governed not only by reflective processes, but also by implicit or automatic affective reactions (Hoffman et al., 2008). Automatic attitude is thought to result from the positive or negative value that our brain automatically assigns to some concept (e.g., physical activity), without that value being accurately accessible to the cognition resulting in an automatic positive or negative inclination toward this stimulus which influence behavior

(Conroy et al., 2017). Correlational (Marteau et al., 2012) and experimental research has established that automatic attitude toward specific stimuli significantly impact various behaviors, including alcohol consumption (Wiers et al., 2011), smoking (Wittekind et al., 2015), eating habits (Aulbach et al., 2019), anxiety and depressive disorders (Becker et al., 2018; Brockmeyer et al., 2019) with studies also indicating a similar association with physical activity (Chevance et al., 2019). For example, in active individuals, stimuli associated with physical activity attract attention (Berry et al., 2011), trigger positive affective reactions (Calitri et al., 2009; Conroy et al., 2010), and activate approach tendencies (Chevance et al., 2017; Farajzadeh et al., 2023). These automatic reactions are thought to facilitate the translation of intention into action (Rhodes et al., 2022; Kwan & Bryan et al., 2010; Cheval et al., 2024). Conversely, studies indicate that more negative automatic affective evaluations impede physical activity behavior (Pfeffer et al., 2021; Padin et al., 2017). That is, negative automatic responses to physical activity cues, such as fatigue, fear of failure (Taylor et al., 2023), or perceiving the effort as not worth the trouble [Net value (action) = Benefit – Cost] can widen this gap, likely leading to loss of motivation to initiate the action or even respond to environmental stimuli resulting in a decrease goal-directed behavior (e.g., physical activity) or behavioral apathy. In other words, brain needs an approximate anticipation of both costs and benefits to decide approach or avoid a stimulus and subsequently action (people with higher behavioral apathy showed that they have problem in action anticipation, means problem in predicting the amount of effort to plan and prepare for the action). This led us to the idea that individuals with apathy might prefer not to approach activities such as physical activities that cost them effort and possibly affect their attitude toward physical activity (Pessiglione et al., 2020). In fact, the negative implicit value of a physical activity stimulus results in an automatic negative inclination toward this stimulus, hindering the individual to initiate physical activity (Levy &

Dubois, 2006), Literature indicates that apathetic healthy individuals are more sensitive to cues of effort than motivated participants (Bonnelle et al., 2015; Bonnelle et al., 2016), likely affect their attitude toward an action. That is, individuals with higher level of apathy perceive the costs of engaging in tasks more acutely, manifesting as a greater hesitation or reluctance to undertake activities that require significant effort. This has been tested in the context of physical activity and the results showed that apathy predicts the effort-based decision-making for exercise significantly (Col'on-Semenza et al., 2021). These findings are supported by studies on patients with frontotemporal dementia who exhibit a higher tendency to avoid effortful activities, even when those activities could be rewarding (Le Bouc et al., 2023). Increased effort aversion, identified as a significant factor contributing to apathy in these patients, might lead to a lack of motivation to engage in activity (e.g., physical activity) and ultimately results in a sense of apathy toward being active. Other studies also showed that individuals with Parkinson's disease having apathy are avoiding exerting effort for low rewards than are motivated patients (Le Heron et al., 2018). In consistent with mentioned literature, studies of patients with Parkinson's disease and genetic cerebrovascular disease have demonstrated that apathy is associated with blunted pupillary responses to anticipation of reward (Le Heron et al., 2018; Muhammed et al., 2016) likely affecting their attitude toward a behavior such as physical activity. While previous studies have examined the automatic tendency toward physical activity behavior and its relationship with the intention to be active and actual physical activity (Cheval et al., 2014; Cheval et al., 2015; Cheval et al., 2016; Cheval et al., 2018; Farajzadeh et al., 2023), no study has directly assessed its relationship with the syndrome defined as a lack of motivation to initiate behavior. Accordingly, the absence of research directly examining the relationship between automatic tendencies toward physical activity and behavioral apathy highlights an important gap in the literature. Therefore,

investigating whether automatic attitudes toward physical activity may act as a potential mechanism underlying the relationship between apathy and physical activity is important.

Regarding the neural basis of apathy, and given that motivated behaviors such as physical activity rely on neural systems that translate value-based decisions into action through motor output (Le Heron et al., 2018; Le Heron et al., 2019; Costello et al., 2024), relying solely on the behavioral manifestations of apathy and their association with physical activity may not provide a comprehensive understanding of this relationship. To gain deeper insight, it is important to investigate the underlying brain mechanisms, particularly the neurophysiological basis of apathy and the potential role of neural processes in linking apathy to physical activity. However, this first requires examining the relationship between apathy and neurophysiological parameters on one hand, and between physical activity and neurophysiological parameters on the other. This approach can help bridge the gap between observable behavior and underlying brain function, thereby enriching our understanding of how apathy may influence physical activity.

1.5.5. Relationships Between Apathy and Neurophysiological Parameters of M1

M1, situated in the precentral gyrus of the brain's frontal lobe plays a central role in the planning and execution of voluntary movements (Pearson et al., 2000; Sanes et al., 2000), as well as in cognitive processes related to motor action (Bhattacharya et al., 2023). In human M1, these functions rely on two types of regions that are part of different networks (Gordon et al., 2023). Effector-specific regions of M1 integrate information from contralateral M1 and adjacent primary somatosensory area (Gordon et al., 2017; Gordon et al., 2023; Barch et al., 2013) for precise and isolated movements (Gordon et al., 2023). Inter-effector regions are strongly connected with a larger network for controlling the body as a whole. This network includes SMA, anterior cingulate cortex, anterior prefrontal cortex, insula, putamen, thalamus, and cerebellum (Gordon et al., 2023).

M1 directly projects to motoneurons of the spinal cord (Stinear et al., 2009; Strick et al., 2021) and is the main transmitter of motor commands down the corticospinal tract (Bortoff et al., 1993; Chouinard & Paus, 2006). As discussed, apathy as a state characterized by a lack of motivation to initiate or respond to environmental stimuli affects various regions of the brain, however, its influence on the human motor system is not thoroughly understood. Thus, to gain a comprehensive understanding of the neural underpinnings of apathy, it is essential to consider its motor involvement. With this in mind, investigating the mechanisms underpinning apathy by assessing the association between apathy and corticospinal excitability is essential. This builds upon evidence that brain regions such as the SMA, dorsal premotor cortex, and M1 are involved in preparing for effortful responses (Klein-Flügge et al., 2016; Zénon et al., 2015), which are often affected in individuals with behavioral apathy (Bonnelle et al., 2016). In fact, findings indicate that behavioral apathy scores correlate with signal changes recorded by functional MRI in regions implicated in response preparation/anticipation, including the SMA and M1. In addition, decreased structural and functional connectivity between anterior cingulate cortex and SMA were associated with increased behavioral apathy (Bonnelle et al., 2016). More recent evidence further strengthens the rationale for examining motor cortical physiology in relation to apathy. Derosiere et al. (2025) demonstrated that apathy is associated with alterations in distributed fronto-basal ganglia-motor circuits involved in effort-based decision-making, including SMA-M1 pathways, suggesting that both corticospinal excitability and intracortical circuits may be relevant to motivated behavior.

Considering the SMA's role in bridging cognition and action, along with its close anatomical connection to the M1, and the known fact that electrical and magnetic stimulation of the SMA triggers rapid responses in the M1 (Chouinard & Paus, 2006; Tokuno et al., 2000; Matsumoto et al., 2007; Green et al., 2018; Rurak et al., 2021), investigating M1 excitability in

relation to apathy may provide further insight into the motor mechanisms underlying motivated behavior. This is particularly important given the limited research examining the impact of apathy on motor-related brain regions.

On the other side of the equation, it is necessary to determine whether habitual physical activity is related to M1 neurophysiology before considering whether neurophysiological parameters may mediate the relationship between physical activity and apathy. Experimental studies show that aerobic exercise can modulate M1 neurophysiology, as indexed by transcranial magnetic stimulation (TMS), including changes in corticospinal excitability and intracortical inhibitory and facilitatory circuits (Singh et al., 2014; Neva et al., 2017; Neva et al., 2021; El-Sayes et al., 2019), with converging support from recent meta-analytic evidence (Youssef et al., 2024). In addition, habitual physical activity has been linked to differences in M1 circuitry, plasticity responses, and responsiveness to acute exercise (Smith et al., 2021; Lulic et al., 2017). Together, these findings suggest that motor cortical physiology may provide a window into physical activity-related changes in brain function. However, despite evidence from exercise-based and plasticity-inducing paradigms, it remains unclear whether intrinsic neurophysiological properties of the motor cortex are meaningfully associated with habitual physical activity in daily life. Addressing this question is a necessary step toward evaluating whether motor cortical neurophysiology may represent a mechanistic link between physical activity and apathy.

1.6. Purpose and Objectives

This doctoral thesis aims to deepen our understanding of the relationship between apathy and physical activity by examining factors that may underlie or influence this association, including behavioral factors, such as attitudes toward physical activity and neurophysiological factors, such as M1 cortical excitability.

Objective 1: Systematically reviewing the correlation between physical activity and apathy.

Objective 2: Investigating the relationship between behavioral apathy, physical activity levels, and attitude toward physical activity.

Objective 3: Systematically reviewing the potential correlation between physical activity and motor cortex neurophysiology

Objective 4: Investigating the relationship between behavioral apathy and M1 cortical excitability.

1.7. Potential Contribution

Our first systematic review and meta-analysis examined the association between physical activity and apathy, providing insight into whether apathy may hinder efforts to promote physical activity. This work laid the foundation for our next study, which investigates the relationships between behavioral apathy, physical activity, and affective attitudes toward physical activity. Our second systematic review, which focused on the relationship between physical activity and motor cortex neurophysiology, provided insight into how M1 may be related to physical activity. Collectively, these studies provide a roadmap for investigating the relationships between apathy, physical activity, and corticomotor excitability. The current project seeks to deepen our understanding of a potential obstacle to physical activity: apathy. Gaining a better understanding of barriers to physical activity could pave the way for more effective strategies to address this issue.

Chapter 2

Apathy and Physical Activity: A Systematic Review and Meta-Analysis

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2.1. Introduction

Psychological factors are essential to quality rehabilitation interventions.¹ Motivation, for example, defined as the hypothetical construct used to describe the internal and external forces that produce the initiation, direction, intensity, and persistence of behavior,² is a parameter that physiotherapists should consider in their intervention, as it influences the patient's ability to adhere to the prescribed rehabilitation programme.³ While motivation can vary within a physiological range, a patient's pathology can also alter it, leading to ineffective care.⁴ An example of such alteration is apathy, which is conceptualized as a behavioral disorder.^{5,6} In the early 1990s, studies began to consider apathy a syndrome rather than a mere symptom of another condition, redefined as a state of primary motivational impairment characterized by reduced goal-directed behaviors (e.g., lack of productivity, effort, initiative, and perseverance), reduced goal-directed cognitions (e.g., lack of interest in learning new things, in new experiences, lack of concern about one's personal and health problems, reduced socialization), and reduced emotional concomitances of behavior (e.g., flat affect, emotional indifference).^{5,6} To date, the dominant theoretical frameworks still consider three subtypes of apathy: behavioral, cognitive, and emotional.^{7,8} Levy and Dubois⁹ proposed that behavioral apathy is related to difficulties in elaborating the plan of actions necessary for behavior. Cognitive apathy is the inability to self-activate thoughts or self-initiate actions. Emotional apathy is the inability to establish the linkage between emotional signals and behavior.⁹ Dickson and Husain have recently proposed a fourth subtype, social apathy, but further research is required.¹⁰

Apathy occurs across a wide range of neurological and psychiatric disorders,¹¹ including dementia (54%),¹² schizophrenia (47–53%),^{13–15} Parkinson's disease (40%),¹⁶ and stroke (33%).¹⁷ Studies have also observed apathy in healthy young adults (1.5%)¹⁸ and older adults with normal

cognitive function (2–7%).^{19–23} Apathy is associated with lower cognitive performance in older adults with normal cognitive functioning,²⁰ cognitive decline (mild cognitive impairment),²¹ transition to dementia,^{24,25} and dementia severity.^{26,27} Therefore, some studies consider apathy a marker of impending cognitive decline and future risk for dementia.²⁰ Others associate apathy with frailty,²⁶ functional decline,^{27–30} poorer quality of life,^{18,23,31} higher mortality,^{32,33} and higher healthcare costs.³⁴ In addition, some studies suggest that apathy can negatively affect physical activity,^{27–40} which includes exercise, sports, active travel (cycling, walking), household chores, and work-related physical activity.⁴¹ This potential effect of apathy is worth investigating since research now widely recognizes physical activity as one of the top contributors to physical and mental health, improving cognitive functioning,⁴² and reducing rates of cardiovascular disease,⁴³ cancer,⁴⁴ hypertension,⁴⁵ diabetes,⁴⁶ obesity,⁴⁷ depression,⁴⁸ and functional dependence.^{48–50} Despite these benefits, one in four adults fails to meet the recommended levels of physical activity.⁴¹ While the motivational impairment that defines apathy is likely to reduce the engagement in physical activity, there are some discrepancies in the literature, with multiple articles showing no evidence of such a relationship^{51,52} or even supporting the opposite association.⁵³

The main objective of this study was to conduct a systematic review and meta-analysis of the direct relationship between apathy and physical activity. We hypothesized that levels of apathy would be negatively associated with levels of physical activity. Since studies assessing this relationship used different methods and outcome measures in a variety of health conditions, we explored whether apathy measure, physical activity measure (e.g., accelerometers, pedometers, questionnaires), physical activity outcome (e.g., total physical activity, moderate or vigorous physical activity, steps per day), and health status influenced the results. Additionally, since

reduced physical activity⁵⁴ and higher apathy^{55,56} are associated with older age and being a woman, we explored whether these demographics influenced the results.

2.2. Methods

2.2.1. Search Strategy

This review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁵⁷ We identified potential studies by searching the MEDLINE (via PubMed), PsycINFO, Web of Science, Embase, SPORTDiscus, and CINAHL databases. The search terms used to identify relevant studies were variants of physical activity (e.g., physical activity, physical education, training, physical fitness, exercise, sport, walk) and apathy (e.g., abulia, apathetic, amotivation, avolition, neuropsychiatric inventory, NPI [NeuroPsychiatry Inventory], emotional indifference, Frontal Lobe Personality Scale, Lille Apathy Rating Scale [LARS], dementia apathy interview and rating, Dementia Apathy Interview and Rating [DAIR], Frontal System Behavior Scale [FrSBe], Key Behaviors Change Inventory [KBCI], Apathy Evaluation Scale, Apathy Scale, and Irritability Apathy Scale. We searched articles up to October 10, 2023, with no limitation on the start date, and used a filter to limit the search to studies published in English. To reduce literature bias, we pre-registered this systematic review in PROSPERO (CRD42023492162).⁵⁸

2.2.2. Eligibility Criteria and Study Selection

2.2.2.1. Inclusion Criteria

To be included in this systematic review, articles had to (1) be published in a peer-reviewed journal, (2) be written in English, (3) report original data collected from human participants, (4) include at least one self-reported measure of apathy and at least one measure of physical activity,

and (5) formally test the association between these two variables (e.g., reporting Pearson's r or Spearman's ρ correlation coefficient). The physical activity measure could be a self-reported measure or device-based measure (e.g., accelerometry) of the level of physical activity. We included cohort studies, baseline data from clinical trials, and cross-sectional studies in this review. The inclusion criteria did not impose any specific age or gender restrictions.

2.2.2.2. Exclusion Criteria

We excluded studies if they were (1) published as a book chapter, study protocol, or conference abstract, or (2) based on laboratory-based measures of physical fitness (e.g., maximal muscle force, 'VO2 max) and not on a measure of physical activity.

2.2.2.3. Study Selection

We screened the articles using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), a web-based collaborative software platform that streamlines the production of systematic reviews. After removing duplicates, two reviewers who authored this article (AF, AH) independently reviewed the titles and abstracts according to the inclusion and exclusion criteria. If there was any doubt about the inclusion or exclusion of an article, the reviewers read the full text. In addition, we performed reference screening and forward citation tracking on the included articles. We resolved disagreements between the two reviewers by consensus among four reviewers (AF, AH, MB, MPB).

2.2.3. Data Extraction

Data extracted from the selected articles included first author's name, article title, publication year, number of participants, number of men and women, mean age and range, health status, type of apathy measure, level of apathy, type of physical activity measure and out-come, level of physical activity, as well as statistical estimates, and significance of the association

between apathy and physical activity. We developed the data extraction form and previously tested it in a systematic review.^{59,60}

2.2.4. Bias Assessment

We assessed the included studies for methodological quality using 10 questions from the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.⁶¹ Two reviewers (AF, AH) independently answered these questions for each study, with a third reviewer (MPB) involved in case of disagreement.

2.2.5. Meta-Analysis

We conducted all analyses in RStudio integrated development environment (IDE) (2023.06.1+524, “Mountain Hydrangea” release) for R software environment⁶² using the meta,⁶³ metasens,⁶⁴ and metafor^{65,66} R packages.

2.2.5.1. Main Meta-Analysis

In the main meta-analysis, we pooled Pearson product-moment correlations from eligible studies to examine the relationship between apathy and physical activity. When a correlation coefficient was not reported, but the exact p-value (or t-value) and sample size were available, and it was possible to know the sign of the correlation, we computed the Pearson’s r-value using an ad-hoc R code using the “qt” function of the R “MASS” package to find the critical value of t.^{67,68} For the studies that reported a relative p-value < 0.001 instead of an exact p-value, we used a p-value of 0.0009 to estimate an approximate r-value. When an article did not report exact p-values but the sample size (n) and Pearson’s correlation coefficient were available, we computed the exact p-value using an ad-hoc R code. We pooled correlations using the generic inverse pooling method via the “metacor” function in the R meta package.⁶³ This function automatically performs

a necessary Fisher's z-transformation on the original, untransformed correlations prior to pooling. The "metacor" function reconverts the pooled association back to its original form for ease of interpretation. We anticipated considerable between-study heterogeneity and therefore used a random-effects model to pool correlations. We used the restricted maximum likelihood estimator⁶⁹ to calculate the heterogeneity variance τ^2 . In addition to τ^2 , to quantify between-study heterogeneity, we report the I^2 statistic, which provides the percentage of variability in the correlations that is not caused by sampling error.⁷⁰ We interpreted the I^2 statistic as follows: 0–40%, may not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; and 75–100%, may represent considerable heterogeneity. To reduce the risk of false positives, we used a Knapp-Hartung adjustment⁷¹ to calculate the confidence interval around the pooled association. We also report the prediction interval, which provides a range within which we can expect the associations of future studies to fall based on the current evidence. If significant, we interpreted the pooled correlation using Cohen's conventions:⁷² $r \approx -0.10$, small negative correlation; $r \approx -0.30$, moderate negative correlation; $r \approx -0.50$, large negative correlation.

2.2.5.2. Publication Bias Assessment

Publication bias refers to the fact that studies with positive or significant results are more likely to be published, while studies with negative or non-significant results are less likely to appear in the literature. Therefore, publication bias can affect the validity and generalization of conclusions of a meta-analysis.⁷³ Here, we assessed publication bias using a funnel plot, which is a scatterplot of the studies' effect size expressed as the Fisher's z-transformed correlation on the x-axis against a measure of their standard error (which is indicative of precision of the study's effect size) on the y-axis. We also used Egger's regression to formally test funnel plot's

asymmetry.⁷⁴ Because the probability of obtaining significant results rises with a larger sample size, publication bias will disproportionately affect small studies. Rücker's limit meta-analysis method explicitly accounts for the publication bias due to small studies,⁷⁵ so we used it to compute a bias-corrected estimate of the true effect size. More specifically, the model underlying Rücker's method is an extended random-effects model that takes account of possible small study effects by allowing the tested effect to systematically depend on the standard error.

Another method used to assess publication bias was p-curve analysis.⁷⁶ When the null hypothesis is true (i.e., there is no true effect), p-values are assumed to follow a uniform distribution: Highly significant effects (e.g., $p=0.01$) are as likely as barely significant effects (e.g., $p=0.049$). However, when the null hypothesis is false (i.e., there is a true effect in our data), p-values are assumed to follow a right-skewed distribution: Highly significant effects are more likely than barely significant effects. A left-skewed distribution would suggest that some studies used statistical tests to find significant results in ways that may not be reproducible or generalizable (i.e., p-hacking).

2.2.5.3. Secondary Meta-Analysis

We conducted a secondary meta-analysis using the same approach as described in the main meta-analysis, but based on Spearman's ρ values, to further test the relationship between apathy and physical activity. We chose not to compare r and ρ values, or any transformed versions of them in the same meta-analysis, because they do not reflect the same property of the data. In the secondary meta-analysis, some studies reported multiple outcomes for the same sample of participants. Therefore, we nested correlation estimates within studies using the "cluster" argument to account for the dependencies between these estimates, resulting in a three-level meta-analysis (level 1: participants, level 2: correlation estimates, level 3: studies). We assessed the distribution

of variance across levels using the multilevel version of I^2 ,⁷⁷ and assessed and compared the performance of the two-level and three-level meta-analyses using the metafor R package.^{65,66}

2.2.5.4. Subgroup Meta-Analyses and Meta-Regressions

We examined subgroup meta-analyses on the differences in correlations between studies that included participants with different health conditions, used different types of physical activity outcomes, and used different types of apathy measures. We also examined meta-regressions on whether the average age of participants or the proportion of women in a study predicted the reported correlation between apathy and physical activity. We used another meta-regression as a sensitivity analysis to examine whether the quality of the studies affected the correlation.

2.3. Results

2.3.1. Literature Search

The primary search identified 6,950 potentially relevant articles from the six databases ([Figure 1](#)), including 2,025 duplicates. Of the 4,925 articles screened, 3,441 were unrelated to apathy or physical activity. Of the remaining 1,484 articles, 65 met the criteria for further investigation and potential inclusion. To increase the completeness of our review, we emailed the corresponding authors of 42 articles that did not formally test the association between apathy and physical activity to request the correlation estimate or raw data so we could compute this estimate ourselves. Six authors replied: one provided raw data,⁷⁸ one provided the Pearson's correlation coefficient,⁷⁹ and four replied that they would contact their coauthors but did not get back to us.^{80–}

⁸³ Reference screening and forward citation tracking identified three additional studies,^{84–86} of which one provided the Pearson correlation upon request.⁸⁴ We provide detailed reasons for exclusion at each stage in the PRISMA flow diagram (Figure 1). Ultimately, we included 28 articles in the systematic review. Two of these articles, published by the same group, had similar methods

and partly overlapping recruitment periods, suggesting that some participants may have been included in both studies.^{52,87} Quality score of studies ranged from 6 to 10 out of 10, with a mean 8.4 (SD 1.2) (Table 1).

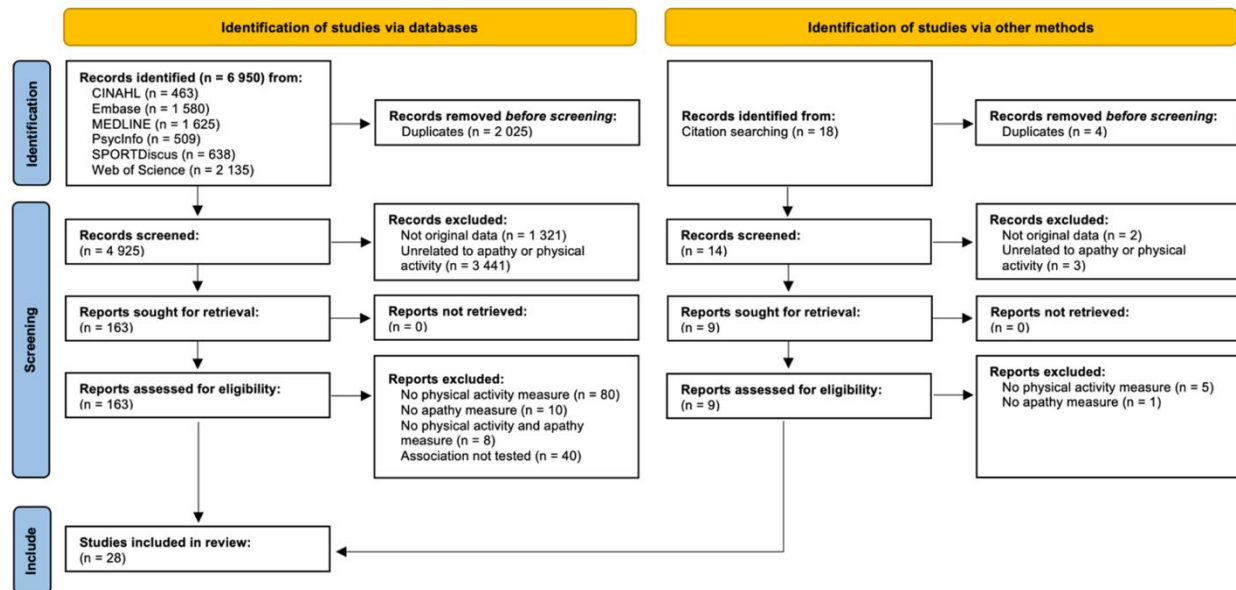


Figure 1. PRISMA 2020 flow diagram.

2.3.2. Descriptive Results

2.3.2.1. Participants

The 28 articles identified by the systematic review included a total of 13,716 participants aged 30 to 95 years, including 7,167 women, 6,283 men, and 266 participants whose gender and sex were not reported. The studies investigated populations with stroke ($k = 4$),^{52,53,87,88} multiple sclerosis ($k = 1$),³ Parkinson's disease ($k = 6$),^{40,84,86,89–91} mental illness ($k = 2$),^{92,93} cancer ($k = 1$),⁹⁴ myotonic dystrophy ($k = 1$),⁵¹ Alzheimer's disease ($k = 1$),³⁹ depression ($k = 3$),^{85,95,96} cognitive impairment ($k = 3$),^{78,79,97} as well as healthy older adults ($k = 9$)^{38,95–102} (Table 1).

2.3.2.2. Apathy

In 14 of the 28 studies, researchers assessed apathy using the Apathy Scale ($k = 13$)^{40,52,84–87,89–91,94–96,100} or its shorter version (12-item Apathy Scale [$k = 1$]).³⁸ This scale consists of 14

questions rated on a Likert scale ranging from 0 (not at all) to 3 (a lot). The total score on the 14-item Apathy Scale ranges from 0 to 42, with higher scores indicating more severe apathy. In clinical settings, a patient with a score ≥ 16 is considered apathetic.¹⁰³ Studies also assessed apathy using the Apathy Evaluation Scale($k = 6$)^{37,51,53,79,88,93} or its shorter version [12-item Apathy Evaluation Scale ($k = 1$)].⁹² This scale consists of 18 items assessing the cognitive, emotional, and behavioral aspects of apathy, rated on a Likert scale ranging from 1 (not at all) to 4 (a lot). The total score ranges from 18 to 72, with higher scores indicating more severe apathy. In a clinical setting, a patient with a score ≥ 37 is considered apathetic.¹⁰⁴ The other measures that researchers used are the apathy subscale of the Geriatric Depression Scale ($k = 4$)^{98,99,101,102} and the apathy subscale of the Neuropsychiatric Inventory Questionnaire ($k = 3$).^{39,78,97} Eighteen studies reported mean levels of apathy (Table 1). The Apathy Scale-based studies revealed a range from 8.7⁴⁰ to 27.8⁸⁴ while the Apathy Evaluation Scale studies reported levels between 13.0⁵¹ and 31.4.⁵³

2.3.2.3. Physical Activity

Twenty-four studies assessed physical activity using a self-reported measure (Table 1). Five of these questionnaire-based studies used the short form of the International Physical Activity Questionnaire (IPAQ-SF),^{51,53,78,89,92} which consists of six items assessing time spent in light (i.e., walking), moderate (e.g., carrying light loads, cycling at moderate speed, doubles tennis), and vigorous physical activity (e.g., digging, fast cycling, heavy lifting, aerobics) over the last seven days.¹⁰⁵ The other questionnaires used to assess physical activity were the long form version of the IPAQ (IPAQ-LF)($k = 4$),^{85,86,95,96} the modified Baecke Habitual Physical Activity Questionnaire (BHPAQ) ($k = 2$),^{38,100} the Minnesota Leisure Time Physical Activity Questionnaire($k = 1$),⁸⁶ the Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (LAPAQ) ($k = 1$),⁹⁹ the National Health Interview Survey and the Minnesota Heart Survey Physical Activity

Questionnaire (NHIS/MHSPAQ) (k = 1),⁹⁷ the Nurses' Health Study II Activity and Inactivity Questionnaire (NHST II Activity) (k = 1),⁹⁴ the Physical Activity Disability Scale (PADS) (k = 1),³⁷ the Nord-Trøndelag Health Study-derived questions (HUNT) (k = 2),^{88,93} the Canadian Community Health Survey-derived questionnaire (CCHS) (k = 1),⁸⁴ and the Physical Activity Scale for the Elderly (PASE) (k = 1).⁴⁰

The studies also assessed physical activity with devices such as accelerometers measuring accelerations in three dimensions (k = 4)^{39,51,79,92} and pedometers measuring the number of steps (k = 3)^{52,53,87} (Table 1). Participants wore these devices at the hip (k = 2),^{51,53} chest (k = 1),⁷⁹ wrist (k = 2),^{39,92} or pocket (k = 1),⁵² and one study did not report where the device was worn.⁸⁷ Studies based on accelerometer-derived measures used an ActiGraph device (ActiGraph, LLC, Pensacola, FL, USA),^{51,79} the Polar M200 (Polar Electro Oy, Kempele, Finland),⁹² or the Micro Motionlogger Watch (Ambulatory Monitoring, Ard-sley, NY, USA).³⁹ The pedometers used were the Omron Walking Style Pro 2.0 (Omron Healthcare, Kyoto, Japan),⁵³ or the Yamasa EX-300 (Yamasa, Choshi, Japan).⁵² One study did not specify the pedometer that was used.⁸⁷

To assess physical activity, the studies used the following outcomes: score from a questionnaire (e.g., PASE, PADS, BHPAQ) (k = 11),^{37,38,40,84,88,91,97-101} MET-min/week (k = 7),^{38,53,85,94-96,100} steps per day (k = 3),^{52,53,87} active time per day or week (k = 8),^{51,84,86,89,90,92,93,102} counts per minute (k = 1),³⁹ kilocalories per day (k = 1).⁷⁹ Four studies used multiple physical activity outcomes (k = 4).^{38,53,84,100}

2.3.2.4. Association Between Physical Activity and Apathy

Among the 28 articles included in the systematic review, 5 reported correlation coefficients of the association between physical activity and apathy. Specifically, 2 articles reported at least 1 Pearson's r correlation coefficient^{37,89} and 3 other articles reported at least 1 Spearman's ρ .^{39,53,92}

For 11 studies,^{51,52,79,85,87,88,90,91,93,94,98} we computed the Pearson's r-value using the exact p-value (or t-value) and sample size. We estimated an approximate r-value for 5 studies reporting a relative p-value < 0.001.^{95-97,99,101} Through email correspondence with the authors, we obtained 3 additional Pearson's r-values^{40,78,84} and 1 additional Spearman's ρ -value.⁸⁵ Furthermore, we calculated 1 Pearson's r value based on publicly available data.¹⁰² In total, we used 22 Pearson's r-values from 22 studies^{37,39,51,52,78,79,84,85,87-91,93-101} and 7 Spearman's ρ -values from 4 studies^{39,53,84,92} in the meta-analysis (Table 1).

The remaining three studies did not report a correlation coefficient, and therefore we did not include them in the meta-analysis. Two of these studies reported a significant negative association between physical activity and apathy based on odds ratios¹⁰⁰ or standardized beta coefficient (β).³⁸ The third study reported only a relative p-value > 0.05.⁸⁶

Table 1. Characteristics of the studies included in the systematic review

Study (Year)	N (# women)	Mean age (SD/range)	Health status	Mean apathy (SD or range)	Mean physical activity (SD or range; measure)	Correlation	p- value	Quality score
Abrantes (2012)	45 (15)	66.1(7.6)	Parkinson's disease	10.7 (6.8; AS)	n.a. (IPAQ-SF)	$r = -0.25$	0.098 [‡]	9
Ayari (2023)	23 (16)	78 (7)	Cognitive impairment	0.17 (NPI-apathy subscale)	451.08 MET-min/week (IPAQ-SF)	$r = -0.48$	0.020 [‡]	9
Farholm (2017)	106 (65)	45.7 (11.9)	Mental illness	n.a. (S-AES)	39.3(52.3, min/day; IPAQ-SF) 44.9(34.2; min/day; wrist accelero.)	$\rho = -0.49$ $\rho = -0.39$	<0.001 <0.01	9
Friedmann (2015)	40 (29)	80.72 (9.3)	Cognitive impairment	17.1 (0.6; AES)	107.4 (10.4; kcal/day; chest accelero.)	$r = -0.04^{\dagger}$	0.821	10
Gorzkowska (2020)	134 (61)	65.2 (9.2)	Parkinson's disease	n.a. (AS)	n.a. (IPAQ, MLTPAQ)	n.a.	<0.05	9
Groeneweg-Koolhoven (2016)	266 (n.a.)	n.a. (>60)	Depressed older adults	n.a. (AS)	n.a. (IPAQ)	$B = -0.9$ $\beta = -0.1$ $OR = 0.5$ $r = -0.12^{\dagger}$	0.05	9
Grool (2014)	4354 (2548)	76 (5.4)	Older adults	n.a. (dichotomized; GDS-apathy subscale)	n.a. (ad-hoc questionnaire)	$r = -0.05^{\dagger}$	<0.001	7
Hamre (2021)	101 (21)	55.5 (11.4)	Stroke	28.0 (7.8; AES)	2.1 (0.3; HUNT-derived questions)	$B = -0.02$ $r = -0.32^{\dagger}$	0.001	10
Hashimoto (2016)	213 (114)	68.9 (7.5)	Older adults	n.a. (AS)	n.a. (modified BHPAQ) Leisure (5-point scale) work (5-point scale) sport (< vs. ≥ 4 MET-h/week)	$OR = 0.59$ n.a. n.a.	<0.05 >0.05 >0.05	6
Henstra (2018)	243 (161)	75.8 (7.0)	Older adult fallers	n.a. (dichotomized; GDS-apathy subscale)	n.a. (ad-hoc questionnaire)	$r = -0.15^{\dagger}$	0.016	9
Henstra (2019a)	380 (247)	69 (11)	Healthy and depressed older adults	n.a. (dichotomized; AS)	2231 (1989; MET-min/week; IPAQ)	$B = -59.8$ $r = -0.17^{\dagger}$	<0.001	6
Henstra (2019b)	2893 (1416)	73.3 (6.6)	Older adults	n.a. (dichotomized; GDS-apathy subscale)	135.4 (80.8; LAPAQ)	$r = -0.06^{\dagger}$	<0.001	10
Henstra (2022)	394 (278)	69.3 (6.9)	Healthy and depressed older adults	n.a. (AS)	n.a. (IPAQ; low vs. moderate vs. high)	$r = -0.17^{\dagger}$	<0.001	6
Ersöz Hüseyinsinoğlu (2017)	85 (35)	64.7 (10.2)	Stroke	31.4 (11.9; AES)	2646.5 (1235.6; daily step; pedo.) 1.8 (1.0 distance count; pedo.) 425.9 (541; MET-min/week; IPAQ-SF)	$\rho = -0.15$ $\rho = 0.01$ $\rho = -0.11$	0.42 0.92 0.29	10
Ishimaru (2020)	43 (35) 20 (14)	90.2 (6.4) 87.5 (6.1)	Severe Alzheimer Moderate Alzheimer	n.a. (NPI-Apathy subscale) n.a. (NPI-Apathy subscale)	73.5 (39.1; counts/min; wrist accelero.) 92.1 (27.9; counts/min; wrist accelero.)	$\rho = -0.71$ n.a.	>0.05 >0.05	9
Ito (2020)	60 (22)	63.7 (14.4)	Stroke	n.a. (dichotomized; AS)	5772(2805; daily steps; pedo.)	$r = -0.32^{\dagger}$	0.013	7
Ito (2021)	101 (36)	64.5 (13.5)	Stroke	10.6 (6.7; AS)	6184 (2914; daily steps; pedo.)	$B = 0.48$ $\beta = 0.05$ $r = 0.05^{\dagger}$	0.64	8
Knak (2020)	67 (32)	41 (10)	Myotonic dystrophy	13 (15.9; AES)	485(144; min/week; hip accelero.) 441(382; min/week; IPAQ-SF)	$\beta = -4.36$ $r = -0.17^{\dagger}$	0.16 n.a.	8
Krell-Roesch (2023)	3222 (1433)	79.2 (65.6)	Healthy and MCI older adults	188 (6; NPI-Apathy subscale)	6.5 (3.9) (NHIS/MHS PAQ)	$OR = 0.89$ $r = -0.32^{\dagger}$	<0.001	8
Lemij (2023)	239 (239)	74.7 (4.4)	Cancer	n.a. (AS)	28.9 (35; MET-h/week; NHST II)	$\beta = -0.43$	0.236	9

						$r = -0.08^{\dagger}$		
Miura (2014)	32 (22)	67.8 (7.4)	Parkinson's disease	n.a. (AS)	n.a. (dichotomized; ad-hoc questions)	$r = -0.12^{\dagger}$	0.510	7
Ng (2021)	121 (47)	64.48 (8.2)	Parkinson's disease	8.7 (6.28; AS)	161.2 (89.5; PASE)	$r = -0.23$	0.011 [‡]	8
Ringen (2018)	83 (26)	40 (11.7)	Mental illness	22.0 (6.4; AES)	3.5 (2.7; h/week; HUNT questions)	$r = -0.24^{\dagger}$	0.028	10
Rios Romenets (2015)	33 (14)	63.8 (9.2)	Parkinson disease	27.8 (7.4; AS)	n.a. (yes vs. no; CCHS questions)	$\rho = -0.31$	>0.05	10
					n.a. (h/week; CCHS derived questions)	$r = -0.18$	0.316 [‡]	
Sacheli (2018)	17 (4)	62.7 (6.1)	Parkinson's disease	7.8 (2.9; AS)	Active: 476.3 (63.1; diary min/week)			
		68.8 (4.7)	Parkinson's disease	15.5 (7.1; AS)	Sedentary: 104.2 (63.1; diary min/week)	$r = -0.40^{\dagger}$	0.011 [‡]	8
Talamonti (2022)	41 (26)	66.93 (5.3)	Healthy older adults	n.a. (GDS-apathy subscale)	n.a. (dichotomized; ad-hoc questions)	$r = -0.25$	0.67	7
Vanner (2008)	43 (31)	53.7 (10.2)	Multiple sclerosis	30.8 (9.3; AES)	10.6 (57.9; PADS)	$r = -0.278$	0.071	9
Yao (2015)	317 (180)	64.5 (10.2)	Healthy older adults	467 (113; AS)	n.a. (modified BHPAQ)			8
					Leisure (5-point scales)	$\beta = -0.25$	<0.001	
					work (5-point scales)	$\beta = -0.05$	>0.05	
					sport (dichotomized; MET-h/week)	$\beta = -0.09$	>0.05	

Notes. Accelero. = accelerometer, AES = Apathy Evaluation Scale, AS = Apathy Scale, B = unstandardized regression coefficient, BHPAQ = Baecke questionnaire on Habitual Physical Activity, CCHS = Canadian Community Health Survey, GDS = Geriatric Depression Scale, HUNT = Nord Trøndelag Health Study, IPAQ = International Physical Activity Questionnaire, LAPAQ = LASA Physical Activity Questionnaire, MCI = Mild Cognitive Impairment, MLTPAQ = Minnesota Leisure Time Physical Activity Questionnaire, n.a. = not available, NHIS/MHS PAQ = National Health Interview Survey and the Minnesota Heart Survey Physical Activity Questionnaire, NHST II = Nurses' Health Study II Activity and Inactivity Questionnaire, NPI = Neuropsychiatric Inventory Questionnaire, OR: Odds Ratio, PADS = Physical Activity Disability Scale, PASE = Physical Activity Scale for the Elderly, pedo. = pedometer, r = Pearson's correlation coefficient, S-AES = Short Apathy Evaluation Scale, β = standardized regression coefficient, ρ = Spearman's correlation coefficient. [†]When Pearson's correlation coefficient (r) was not reported in an article, but the exact p-value and sample size (n) were available and it was possible to know the sign of the correlation based on the information provided in the article, the r value was computed using an ad-hoc R code. [‡]When exact p-values were not reported in an article, but the sample size (n) and Pearson's correlation coefficient r were available, the exact p-value was computed using an ad-hoc R code. For the studies that reported a relative p-value < 0.001 instead of an exact p-value, we used a p-value of 0.0009 to estimate an approximate r value

2.3.3. Meta-Analysis

2.3.3.1. Main Meta-Analysis

Our meta-analysis of 22 studies (N = 12,541) based on Pearson's r-values revealed a statistically significant small negative correlation between apathy and physical activity ($r = -0.13$; 95% CI: $-0.18, -0.09$; $p < 0.0001$; see Table 2 and [Figure 2](#)). Further supporting this result between-study statistical heterogeneity could be considered moderate ($\tau^2 = 0.0038$; 95% CI: $0.0003, 0.0167$; $I^2 = 49.0\%$; 95% CI: $16.4, 68.9$), and the prediction interval ranged from $r = -0.26$ to 0.00 , suggesting that the correlation would be negative for a future study.

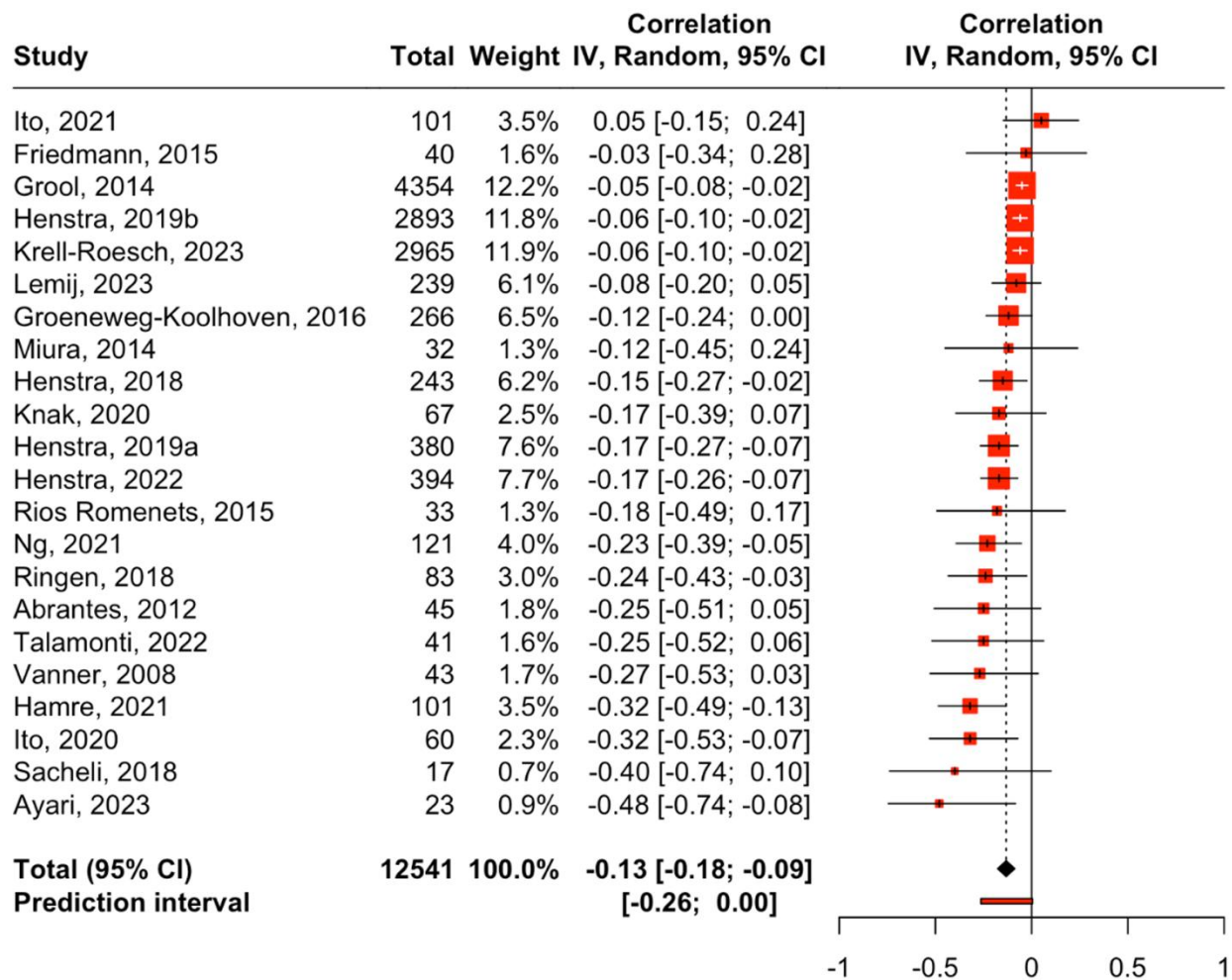


Figure 2. Main meta-analysis. Correlation between apathy and physical activity based on Pearson's r values ($k = 22$, $n = 12,541$). CI = confidence interval, IV = inverse variance

2.3.3.2. Publication Bias Assessment

The funnel plot showed an asymmetrical pattern ([Figure 3a](#)), with more studies on the left of the vertical dashed line representing the average effect size. In addition, if we input the missing studies in the right part of the plot to increase the symmetry, most of these studies would lie in the non-significance region (in white), which suggests that the asymmetry in the funnel plot may be caused by publication bias rather than other potential causes, such as different study procedures and between-study heterogeneity. Egger's regression test confirmed that the data in the funnel plot was asymmetric ($b = -1.44$; 95% CI: $-1.97, -0.91$; $p = 3.1 \times 10^{-5}$). However, the bias-corrected estimate of the true effect size, calculated using Rücker's limit meta-analysis method, showed that the small correlation reported in the main analysis would remain significant even if such publication bias was present in our data set ($r = -0.08$; 95% CI: $-0.14, -0.02$; $p = 0.0065$).

We provided 29 correlation values (Pearson's r or Spearman's ρ) to the p-curve analysis ([Figure 3b](#)). The observed p-curve included 14 statistically significant results ($p < 0.05$), 13 of which were highly significant ($p < 0.025$). The p-value of the right-skewness test was < 0.001 for both the half curve (curve of p-values ≤ 0.025) and the full curve (curve of p-values < 0.05), confirming that the p-curve was right-skewed and suggesting that the effect of our meta-analysis is true, i.e., that the effect we estimated is not an artifact caused by selective reporting (e.g., p-hacking) in the literature.¹⁰⁶ In addition, the statistical power of the studies that were included in the p-curve analysis was 90% (90% CI: 77, 97), suggesting that approximately 90% of the significant results are expected to be replicable.

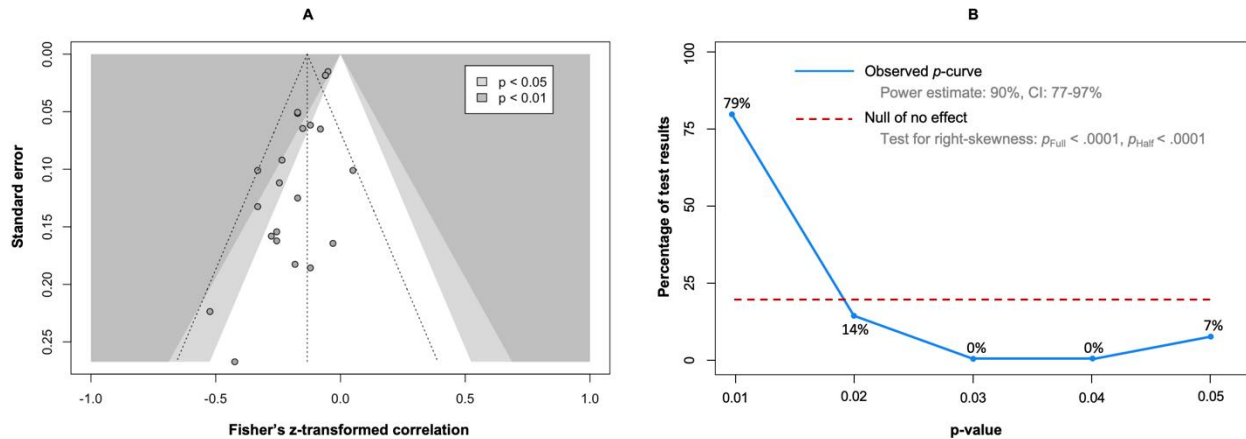


Figure 3. Publication bias assessment. Contour-enhanced funnel plot of the main meta-analysis (A). The vertical dashed line represents the average effect size. The two other dashed lines represent the idealized funnel-shape that studies are expected to follow. When there is no publication bias, the data points in a funnel plot should form a roughly symmetrical, upside-down funnel. Studies in the top part of the plot, which have lower standard errors, are expected to lie closely together, and not far away from the pooled effect size. In the lower part of the plot, studies have higher standard errors, the funnel “opens up,” and effect sizes are expected to scatter more heavily to the left and right of the pooled effect. **P-curve analysis (B).** The blue line indicates the distribution of the analyzed p-values. The red dotted line illustrates a uniform distribution of the p-values, indicating the absence of a true effect.

2.3.3.3. Secondary Meta-Analysis

Results of the secondary meta-analysis based on Spearman’s ρ -values ($k=4$, $n=543$) were consistent with those based on Pearson’s r as they showed a statistically significant moderate to large negative correlation between apathy and physical activity ($r=-0.40$; 95%CI: $-0.68, -0.02$; $p=0.043$) (Figure 4). However, we observed substantial to considerable between-study statistical heterogeneity (between-cluster $\tau^2=0.09$; 95%CI: $0.01, 0.97$; $I^2=82.0\%$; 95%CI: $64.1, 91.0$), and the prediction interval ranged from $r=-0.87$ to 0.45 , indicating that a moderate to large positive correlation can not be ruled out for future studies. The sampling error variance on level 1 and the value of I^2 on level 2 (i.e., the amount of heterogeneity variance within studies) were small (12.4% and $3.5 \times 10^{-9} \%$, respectively). The largest share of heterogeneity variance was from level 3, with between-study heterogeneity making up 87.6% of the total variation in our data. Overall, this

indicates that there is considerable between-study heterogeneity, and that little variance results from differences within studies. However, the three-level model showed a better fit than the two-level model with lower Akaike's information criterion (AIC) (3.2 vs. 6.6) and Bayesian information criterion (BIC) (2.6 vs. 6.2), indicating better performance. These lower AIC and BIC are consistent with the significant likelihood ratio test comparing the two models ($\chi^2 = 5.35$; $p = 0.0207$). Therefore, although the three-level model introduces an additional parameter, this added complexity has improved our estimate of the pooled effect.

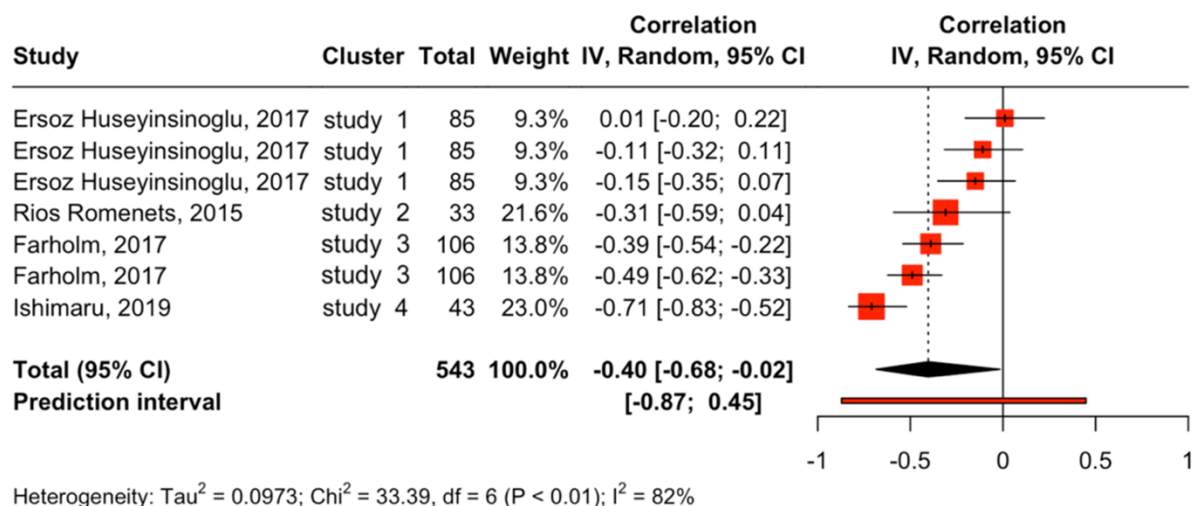


Figure 4. Secondary meta-analysis. Correlation between apathy and physical activity based on Spearman's rho values ($k = 7$, $n = 437$). CI = confidence interval, IV = inverse variance.

2.3.3.4. Subgroup Meta-analyses

To test for subgroup differences between health status, we compared studies comprising older adults who were healthy, depressed, fallers, or had mild cognitive impairment ($k = 10$), people with Parkinson's disease ($k = 5$), and stroke survivors ($k = 3$). We found statistical difference between these studies ($p < 0.0001$) (Table 2;). The relationship between apathy and physical activity was statistically significant in studies that included older adults ($r = -0.10$; 95% CI: $-0.15, -0.05$) or patients with Parkinson's disease ($r = -0.22$; 95% CI: $-0.31, -0.14$), but not in studies that included stroke survivors ($r = -0.20$; 95% CI: $-0.64, -0.34$). However, statistical

power was lacking in the latter ($k = 3$) and other health status ($k = 1$). To test subgroup differences between physical activity outcomes, we compared studies using a score from a questionnaire ($k = 7$), MET-min per week ($k = 6$), active time per day or week ($k = 5$), and steps per day ($k = 2$) (Table 2;). We found statistical difference between these studies ($p < 0.0001$). The relationship between apathy and physical activity was statistically significant in studies using a score ($r = -0.14$; 95% CI: $-0.23, -0.04$), MET-min/week ($r = -0.15$; 95% CI: $-0.22, -0.08$), and active time ($r = -0.22$; 95% CI: $-0.30, -0.14$), but not in studies that used the number of steps per day ($r = -0.13$; 95% CI: $-0.99, 0.98$). However, statistical power was lacking in the latter ($k = 2$) and other physical activity outcomes ($k = 1$). To test for subgroup differences between apathy measures, we compared studies using the Apathy Scale ($k = 11$), the Apathy Evaluation Scale ($k = 5$), the apathy subscale of the Geriatric Depression Scale ($k = 4$), and the apathy subscale of the Neuropsychiatric Inventory Questionnaire ($k = 2$) (Table 2;). The relationship between apathy and physical activity was statistically significant in studies using the Apathy Scale ($r = -0.15$; 95% CI: $-0.20, -0.10$), Apathy Evaluation Scale ($r = -0.23$; 95% CI: $-0.35, -0.11$), and Geriatric Depression Scale ($r = -0.06$; 95% CI: $-0.10, -0.02$), but not in studies that used the Neuropsychiatric Inventory Questionnaire ($r = -0.23$; 95% CI: $-1.00, 0.99$). However, statistical power was lacking in the latter apathy measure ($k = 2$).

Table 2. Results of the main, secondary, and subgroup meta-analyses

	K	N	cor.	95% CI	I ² (%)	P
Main: Pearson's r values						< .0001
Apathy and physical activity	22	12,541	-.13	[-.18 to -.09]	49	
Main: Rücker's limit method						.0065
Apathy and physical activity	22	12,541	-.08	[-.14 to -.02]	49	
Secondary: Spearman's rho values						.043
Apathy and physical activity	4	543	-.40	[-.68 to -.02]	82	
Subgroup: Health status						< .0001
Older adults (healthy, depression, falls, or MCI)	10	11,599	-.10	[-.15 to -.05]	50	
Parkinson's disease	5	248	-.22	[-.31 to -.14]	0	
Stroke	3	262	-.20	[-.64 to .34]	9	
Cancer	1	239	-.08	[-.20 to .05]		
Severe mental illness	1	83	-.24	[-.43 to -.03]		
Myotonic dystrophy	1	67	-.17	[-.39 to .07]		
Multiple sclerosis	1	43	-.27	[-.53 to .03]		
Subgroup: Physical activity outcome						< .0001
Score	7	6,398	-.14	[-.23 to -.04]	56	
MET-min/week	6	1,347	-.15	[-.22 to -.08]	0	
Active time	5	241	-.22	[-.30 to -.14]	0	
Steps/day	2	161	-.13	[-.99 to .98]	81	
Frequency	1	4,354	-.05	[-.08 to -.02]		
Kcal/day	1	40	-.03	[-.34 to .28]		
Subgroup: Apathy measure						< .0001
Apathy Scale (AS)	11	1,688	-.15	[-.20 to -.10]	0	
Apathy Evaluation Scale (AES)	5	334	-.23	[-.35 to -.11]	0	
GDS	4	12,541	-.06	[-.10 to -.02]	22	
NPI	2	2,988	-.23	[-1.00 to .99]	77	

2.3.3.5. Meta-Regressions

Age statistically influenced the correlation values of the meta-analysis studies ($k = 21$; $p = 0.003$) ([Figure 5A](#)), with older samples being associated with more negative relationships between apathy and physical activity. Conversely, the proportion of women did not statistically influence the meta-analysis studies' correlation values ($k = 21$; $p = 0.346$) ([Figure 5B](#)).

2.3.3.6. Sensitivity Analysis

The meta-regression by quality score based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies⁶¹ ($k = 22$) showed that a study's quality did not influence correlation values ($p = 0.986$) ([Figure 5C](#)).

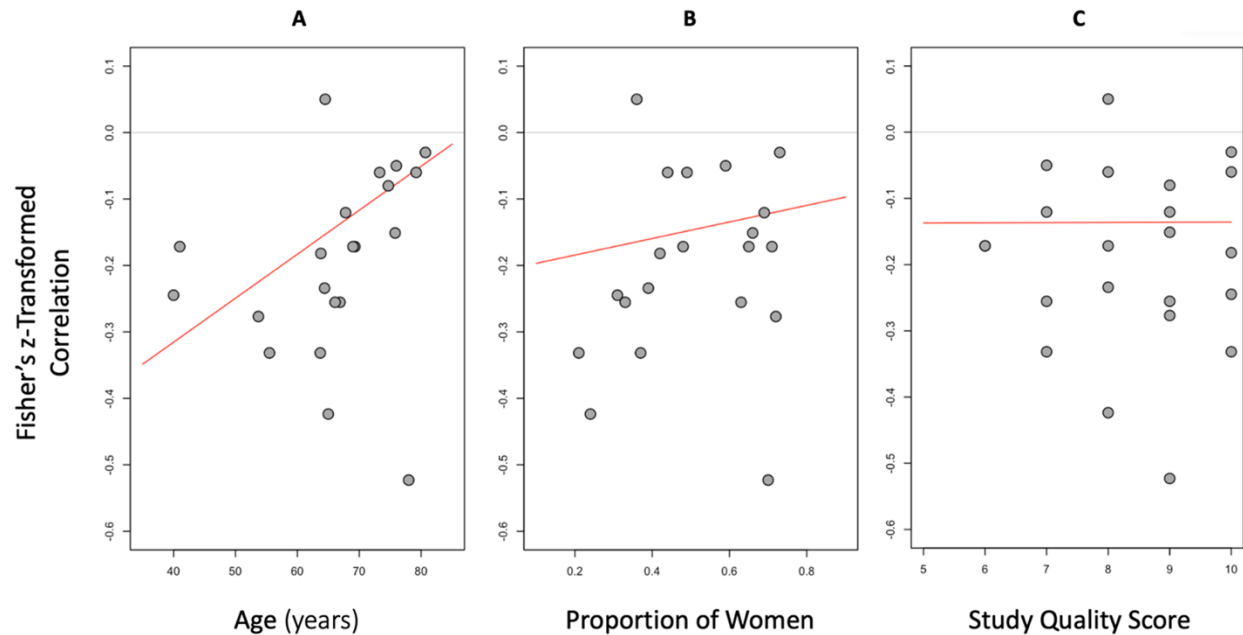


Figure 5. Meta-Regressions testing the influence of age (A), the proportion of women (B), and study quality score (C) on the correlation estimates of the main meta-analysis studies

2.4. Discussion

2.4.1. Clinical Implications

As hypothesized, the main meta-analysis based on Pearson's r -values showed a small negative correlation between apathy and physical activity. The secondary analysis based on Spearman's ρ -values showed a moderate to large negative correlation, further supporting the results. While larger effect sizes may result in more noticeable clinical differences at the individual level and in the short term, smaller effect sizes may also have important clinical implications, especially when considered in the context of population health, prevention strategies, and long-term outcomes. Given the important contribution of physical activity to the primary, secondary,

and tertiary prevention of many diseases including cardiovascular disease,^{107,108} stroke,^{49,109} depression,^{110,111} obesity,¹¹² de-mentia,¹¹³ osteoarthritis,¹¹⁴ and cancer,¹¹⁵ the small effect size we report in the main meta-analysis based on Pearson's r-values may translate into meaningful clinical improvements in patient outcomes. Health professionals have an important role to play in preventing and reducing the detrimental effects of apathy on physical activity. Studies have shown that non-pharmacological interventions such as multisensory stimulation, music therapy, cognitive stimulation, and pet therapy are effective in decreasing apathy.¹¹⁶ Physical therapists can contribute through exercise therapy as intervention studies have shown that exercise can reduce apathy,^{117,118} opening the possibility for a virtuous circle as this reduced apathy can then support physical activity engagement. In patients with apathy, the exercise intervention should take into consideration the reduced motivation, as this will affect the patient's ability to adhere to the prescribed programme.³ Since the perceived cost of physical activity is higher in this population, the therapist needs to find ways to increase the rewards associated with the intervention. These rewards can be intrinsic (e.g., fun activity) or extrinsic (e.g., validation of the progression checks set by the therapist).

2.4.2. Underlying Mechanisms and Health Status

The mechanisms underlying the association between apathy and physical activity remain poorly understood and overlooked. One exception is a recent study showing that weaker intention to be physically active mediated the association between higher levels of behavioral apathy and lower habitual levels of moderate-to-vigorous physical activity.¹¹⁹ In addition, explicit attitudes mediated the effect of behavioral apathy on intentions to be physically active. These findings indicate the involvement of controlled motivational processes, allowing for potential interventions to reduce the detrimental effects of apathy on physical activity. Our meta-analysis observed the

largest significant effect size in patients with Parkinson's disease, which can be used as a model to better understand the mechanisms underlying the association between apathy and physical activity. This association is consistent with the decision theory of goal-directed behavior.¹²⁰ According to this theory, people contrast costs and benefits when considering whether to engage in physical activity. Engagement occurs when the net value of this contrast is beneficial. According to studies of patients with Parkinson's disease, apathy results from dopamine depletion in the brain.^{121–125} When dopaminergic medications address this depletion, studies have shown that patients are more willing to squeeze a handgrip to earn a reward than to decline,¹²⁶ and they exert more force to earn a reward.^{127,128} Taken together, these results suggest that inpatients with Parkinson's disease, apathy may be associated with dopaminergic deficits that could increase the perceived cost of physical effort, thereby decreasing the willingness to engage in physical activity. In addition to patients with Parkinson's disease, our subgroup meta-analyses suggest that the negative relationship between apathy and physical activity is in older adults who were healthy, depressed, fallers, or had mild cognitive impairment. The meta-regression further supports this result, showing that older ages were associated with more negative relationships between apathy and physical activity. The higher metabolic energy associated with a given physical activity in older adults compared to young adults could explain this effect of aging.^{129–131} This decreased efficiency may increase the cost for engaging in physical activity in a non-linear manner across the years, amplifying the impact of apathy on the engagement in physical activity. Moreover, studies suggest that apathy increases with age,⁵⁵ which would further contribute to amplifying the impact of this decreased efficiency on physical activity. Although there was no clear evidence of an association between apathy and physical activity in other health conditions, we cannot rule out such an association, as the lack of statistical significance could result from a lack of statistical power in these health conditions (e.g.,

stroke) or by the impossibility of comparing them with other health conditions in the subgroup meta-analysis, as they were only examined in a single study (e.g., cancer). Contrary to previous studies,^{55,56,132} our results showed no evidence of an effect of gender.

2.4.3. Measures of Physical Activity and Apathy

Both self-reported (e.g., MET-minutes per week) and device-based outcomes (e.g., active time per day or per week) of physical activity were negatively associated with apathy, suggesting that both these approaches can capture this relationship. Apathy was not associated with the number of steps per day, but this analysis may be underpowered because it included only two studies with a total of 161 participants, some of whom may have been included in these two studies from the same group with similar methods and partly overlapping recruitment periods.^{52,87} The three most used measures of apathy (Apathy Scale, Apathy Evaluation Scale, Apathy Subscale of the Geriatric Depression Scale) were all associated with physical activity, further supporting the robustness of this association. Only one measure of apathy showed no evidence of an association with physical activity, but this result was based on only two studies, which both showed a significant negative association.

2.4.4. Limitations

Several limitations impact the results of this systematic review and meta-analysis. (1) We only included articles published in English. Inclusion of articles published in other languages may have influenced the results. (2) Due to the correlational nature of the meta-analyzed results, we cannot conclude a causal relationship between apathy and physical activity, nor can we exclude the possibility that this relationship is indirect, i.e., mediated by other factors. (3) We did not preregister the meta-analysis because the author with this expertise (IML) joined only after we conducted the systematic review. However, since the preregistered systematic review defines the

studies included in the meta-analysis and since the meta R package ⁶³ provides very few degrees of freedom, there was little room for bias in the main and secondary meta-analyses. This reasoning also applies to the subgroup analyses because the studies included in the systematic review imposed the health conditions, types of physical activity measures, measurement instruments, and out-comes, as well as the apathy measurement instruments.(4) A small number of the 43 authors we contacted (3,7%) shared their estimates (2, 5%) or raw data (1, 2%)with us, which is less than reported in previous literature.¹³³ Including these estimates may have influenced our results.

2.5. Conclusion

Our results suggest that higher levels of apathy are associated with lower levels of physical activity and that this negative association is stronger with age. As such, apathy may be a limiting factor to exercise therapy, which is within the scope of practice of physiotherapists,¹³⁴and may have prognostic implications in patients whose condition requires physical activity. Accordingly, physiotherapists should screen for apathy when a patient has difficulty engaging in physical activity, especially patients with Parkinson's disease and older adults, and develop strategies to increase the intrinsic and extrinsic motivation associated with physical activity in those who experience apathy.

2.6. Data Availability

In line with good research practices,¹³⁵ the dataset as well as R and R Markdown scripts are freely available in Zenodo (<https://doi.org/10.5281/zenodo.10929857>).

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Chapter 3

Apathy, Intentions, Explicit Attitudes, and Approach-Avoidance Tendencies in Physical Activity Behavior

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3.1. Introduction

Behavioral apathy is defined as a state of primary motivational impairment characterized by difficulty in elaborating the action plan required for behavior (Levy & Dubois, 2006; Marin, 1990; Marin, 1991). Apathy is observed in a wide range of conditions, including dementia (Leung et al., 2021), Parkinson's disease (den Brok et al., 2015), and stroke (Zhang et al., 2023), and has been associated with frailty (Mega et al., 1996), functional decline (Ayers et al., 2017), poorer quality of life (Groeneweg-Koolhoven et al., 2014), higher mortality (Vilalta-Franch et al., 2012), and increased healthcare costs (Kruse et al., 2023). Additionally, higher levels of apathy have been associated with lower levels of physical activity (Farajzadeh et al., 2024). This association may further compromise the health of individuals with apathy, as insufficient physical activity is known to be associated with cognitive decline (Cheval et al., 2023), cardiovascular disease (Wahid et al., 2016), cancer (Moore et al., 2016), hypertension (Liu et al., 2017), diabetes (Cheval et al., 2021), obesity (Bleich et al., 2018), depression (Boisgontier et al., 2020), and functional dependence (van Allen et al., 2024; van Allen & Boisgontier, 2024). Therefore, understanding the mechanisms underlying the association between behavioral apathy and physical inactivity may contribute to improving the design and specificity of rehabilitation interventions, ultimately improving the condition of individuals with apathy. However, these mechanisms remain largely overlooked and poorly understood. Considering their close relationship with both motivation and physical activity, intentions, explicit attitudes, and approach-avoidance tendencies toward physical activity may play a pivotal role in the relationship between apathy and physical activity engagement.

Intention is thought to capture the motivational factors that influence a behavior and reflects the effort that individuals are willing to invest for the behavior to occur (Ajzen, 2011). This motivational construct is considered the most proximal antecedent of physical activity behavior

(Ajzen, 2011; Biddle et al., 2007). Further, the role of intentions in physical activity engagement is highlighted in a meta-analysis showing that less than 5% of individuals engage in physical activity without intending to be physically active (Feil et al., 2023). However, while intention is necessary to engage in physical activity, it is not sufficient to guarantee this engagement (Rhodes & de Bruijn, 2013). This insufficiency is illustrated by meta-analyses showing that almost half of the individuals who intend to be physically active are unable to fulfill this intention (Feil et al., 2023; Rhodes & de Bruijn, 2013).

In recent years, dual-process models have been developed to address the limitations of social cognitive models in explaining physical activity behavior (Rhodes et al., 2019). These new idiosyncratic models assert that physical activity behavior is governed not only by reflective processes (e.g., intentions, explicit attitudes), but also by automatic processes (e.g., automatic attitudes) (Brand & Ekkekakis, 2017; Cheval & Boisgontier, 2021; 2024; Conroy & Berry, 2017). Reflective processes are typically described as slow, deliberative, inefficient (relying on higher brain functions), and conscious (Strack & Deutsch, 2004), and are typically assessed with questionnaires. However, reflective processes do not always exhibit all these characteristics simultaneously, as certain reflective responses can be efficient or partially automatic (Melnikoff & Bargh, 2018). In contrast, automatic processes are faster and initiated unintentionally, rely on learned associations, do not require conscious awareness, and are most often assessed using reaction times to visual stimuli (e.g., images depicting physical activity vs. sedentary behavior).

Attitude is a psychological tendency to evaluate a stimulus with some degree of favor or unfavor (Eagly & Chaiken, 1993). This tendency is considered an indirect antecedent of physical activity (Brand & Ekkekakis, 2017; Cheval & Boisgontier, 2021; Hagger & Chatzisarantis, 2014), influencing this behavior primarily through its effect on intention (Ajzen, 2011). Attitude can

manifest as reflective (i.e., explicit attitudes) and automatic processes (i.e., automatic attitudes). Explicit attitudes are attitudes that people can report and for which activation can be consciously controlled (Rydell & McConnell, 2006). Automatic attitudes are introspectively unidentified traces of past experience that mediate favorable or unfavorable evaluation of a social object (Greenwald & Banaji, 1995). In other words, an automatic attitude is thought to result from the positive or negative value that our brain spontaneously assigns to some concept (e.g., person, place, or behavior), without that value being accurately accessible to cognition (Conroy & Berry, 2017). This implicit value of a stimulus results in an automatic positive or negative inclination toward this stimulus, which influences behavior. An illustration of this influence is approach-avoidance tendencies, an automatic preparation of the organism to execute a motor pattern toward or away from a behavior (Friesen et al., 2011).

The aim of this study was to examine the relationships between apathy, the intention to be physically active, explicit attitudes toward physical activity, approach-avoidance tendencies toward physical activity and sedentary behaviors, and weekly physical activity engagement. According to a recent meta-analysis (Farajzadeh et al., 2024), we expected behavioral apathy to influence habitual levels of physical activity. Intention is essential for goal-directed behavior (Gollwitzer & Brandstätter, 1997) and a key determinant of physical activity (Ajzen, 1987). Individuals with apathy often have difficulties initiating and maintaining goal-directed actions (Levy & Dubois, 2006; Marin, 1991). Therefore, we hypothesized that intention to engage in physical activity would mediate the relationship between apathy and habitual weekly physical activity engagement. The heightened sensitivity to effort-related cues in individuals with apathy leads them to perceive actions as more costly (Bonnelle, Veromann, et al., 2015; Bonnelle, Manohar, et al., 2016) and is likely to influence explicit attitudes toward physical activity as well

as their antecedents, approach-avoidance tendencies. Therefore, our secondary hypothesis was that the relationship between apathy and intentions to be physically active would be mediated by explicit attitudes and approach-avoidance tendencies.

3.2. Methods

3.2.1. Population

Participants were recruited through social media, posters at the Faculty of Health Sciences, University of Ottawa, and emails to non-profit associations. Inclusion criteria were age 20–90 years and access to a personal computer, a laptop, or a tablet with internet. Informed consent was collected in accordance with the Declaration of Helsinki. The study was approved by University of Ottawa’s Research Ethics Boards (H-05-21-6791). All participants provided informed consent. Data were collected between July 2022 and December 2023. Participants were not compensated for their participation.

3.2.2. Power Analysis

An a priori power analysis was conducted in G*power (Faul et al., 2009) to estimate the minimum sample required for $\alpha = 0.05$, power $(1 - \beta) = 90\%$, and a medium effect size $f^2 = 0.2$ (Cohen, 2013). We used this heuristic value because, at the time the study was designed, no meta-analysis had assessed the effect size of apathy on physical activity or the effect of apathy on the intention to be physically active. The power analysis was based on an F test in a multiple linear regression (R^2 increase) that included the two tested predictors (apathy and approach-avoidance tendencies) and 7 control variables and estimated that a minimum sample size of $n = 67$ was required. The aim of this approach was to ensure that we would have a 90% or greater chance of finding a statistically significant medium effect, if one exists, in each of the paths [i.e., each linear

multiple regression model; Yzerbyt et al. (2018)] of the mediation we described in our main hypothesis. However, because heuristics are a weak justification for determining an effect of interest, we aimed to collect as much data as possible within our time and resource constraints (Lakens,2022). Of note, the meta-analysis by Farajzadeh et al. (2024), published after the data collection for the current study, provided two effect size estimates for the relationship between apathy and physical activity engagement: $r = -0.13$ ($f^2 = 0.017$, based on r values in the literature) and $r = -0.40$ ($f^2 = 0.191$, based on p values in the literature). Using these effect sizes, analyses based on an F test in a multiple linear regression that included one tested predictor (apathy) estimated that a minimum sample size of $n = 58$ to 621 would have been required. Another approach would have been to use the power Mediation R package (Qiu, 2021). However, we decided against this approach because the lack of information available in the literature would have forced us to use heuristics to set the values of several arguments required for the power analysis.

3.2.3. Experimental Protocol

3.2.3.1. Procedures

Participants performed approach-avoidance tasks online using Inquisit 6 software (Millisecond Software,2015), and responded to questions related to apathy, habitual level of moderate-to-vigorous physical activity, age, sex (male, female), gender (man, woman, non-binary, transgender man, transgender woman, other), weight, height, depressive symptoms, and health condition. One attention check question was included in the questionnaires: “Please answer ”5” to this question that allows us to verify that you actually read the questions.”

3.2.4. Self-Reported Variables

3.2.4.1. Behavioral Apathy

Behavioral apathy was assessed using the action initiation subscale of the Lille Apathy Rating Scale (LARS) (Bonnelle, Veromann, et al., 2015; Sockeel, 2006) ([Appendix A](#)). This subscale focuses on everyday productivity and initiative and has been used as an index of behavioral apathy (Bonnelle, Manohar, et al., 2016). This subscale includes 11 questions with responses ranging from 1 (completely untrue) to 7 (completely true), resulting in a total score ranging from 11 to 77. We used the total score in our analyses, with higher scores indicating a higher level of behavioral apathy.

3.2.4.2. Habitual Level of Moderate-to-Vigorous Physical Activity

The habitual level of physical activity was derived from the short form of the International Physical Activity Questionnaire ([IPAQ-SF](#)), a self-administered questionnaire that identifies the frequency and duration of moderate and vigorous physical activity during the past 7 days to estimate habitual level of physical activity and sedentary behavior (Craig et al., 2003). The habitual level of moderate-to-vigorous physical activity (MVPA) in minutes per week was used in the analyses.

3.2.4.3. Explicit Attitudes

Explicit attitudes toward physical activity were calculated as the mean of two items based on two bipolar semantic differential adjectives on a 7-point scale [“unpleasant” (1) – “pleasant” (7); “unenjoyable” (1)– “enjoyable” (7)]. The statement begins with “For me, to participate in regular physical activity is ...” (Farajzadeh et al., 2023; Hoyt et al., 2009). These two scores showed a very strong correlation ($r = .915$; $p < 2.2 \times 10^{-16}$), and their sum was used as an indicator of explicit attitudes in the statistical analyses.

3.2.4.4. *Intention to Be Physically Active*

The intention to be physically active was derived from the response to the question “How much do you agree with the following statement: Over the next 7 days, I intend to do at least 150 minutes of moderate-intensity physical activity; or at least 75 minutes of vigorous intensity physical activity; or an equivalent combination of moderate- and vigorous-intensity physical activity” on a 7-point scale ranging from “strongly disagree” (1) to “strongly agree” (7) (Rhodes & Rebar, 2017).

3.2.4.5. *Depressive Symptoms*

As it has been shown to be associated with apathy (Starkstein et al., 2001), depression needed to be controlled for in our analyses. Depressive symptoms were assessed using the Depression subscale of the Depression Anxiety Stress Scale ([DASS](#)) (Lovibond & Lovibond, 1995). Participants were asked to read 14 statements and indicate how much the statement applied to them over the past week using a 4-point Likert scale ranging from 0 (“did not apply to me at all”) to 3 (“applied to me very much of the time”), resulting in a total score ranging from 0 to 48. We used the total score as a control variable in our analyses, with higher scores indicating greater depressive symptoms.

3.2.4.6. *Chronic Conditions*

Since it has been shown to be related with physical activity (Vancampfort et al., 2017), our analyses included the number of chronic conditions, which was derived from a question based on item PH006 of the Survey of Health, Ageing and Retirement in Europe (Börsch-Supan, 2022). “Has a doctor ever told you that you had any of the following conditions?”. The possible answers were “A stroke or cerebral vascular disease”, “High blood pressure or hypertension”, “High blood cholesterol”, “Diabetes or high blood sugar”, “arthritis, including osteoarthritis, or rheumatism”,

“rheumatoid arthritis”, “chronic lung disease such as chronic bronchitis or emphysema”, “asthma”, “osteoporosis”, “Cancer or malignant tumour, including leukaemia or lymphoma, but excluding minor skin cancers”, “stomach or duodenal ulcer, peptic ulcer”, “Parkinson disease”, “hip fracture or femoral fracture”, “Alzheimer’s disease, dementia, organic brain syndrome, senility or any other serious memory impairment”, “other affective or emotional disorders, including anxiety, nervous or psychiatric problems”, “chronic kidney disease”, “other conditions, not yet mentioned”, and “none”.

3.2.4.7. Approach-Avoidance Tendencies

Approach-Avoidance Task

Approach-avoidance tendencies toward physical activity and sedentary stimuli were tested using an approach-avoidance task, which has shown good reliability ($r = 0.83$) (Farajzadeh et al., 2023) and good validity (Zenko & Ekkekakis, 2019). A video illustrating the task is available online (Boisgontier, 2024). Two experimental conditions and two neutral conditions were tested (Cheval, Tipura, et al., 2018; Farajzadeh et al., 2023; Goubran et al., 2025). In the experimental conditions of this task, a trial starts with a fixation of a cross presented at the center of the screen for a random time ranging from 500 to 750 ms ([Figure 1A](#)). Then, an avatar appears either at the top or bottom third of the screen for one second, before a pictogram representing a physical activity behavior or a sedentary behavior appears in the center of the screen ([Figure 1A](#)). The participant sitting in front of the computer with one index finger positioned on the “U” and the other index finger on the “N” key is instructed that pressing the “U” key moves the avatar up and pressing the “N” key moves the avatar down. Accordingly, the movement of the avatar is always congruent with the pressed key: The top key (i.e., U) moves the avatar up, while the bottom key (i.e., N), moves the avatar down. Importantly, however, the approach or avoidance action depends on the

initial position of the avatar at the beginning of the trial. If the avatar appears below the stimulus, the top key is associated with an approach movement, while the bottom key is associated with an avoidance movement. Conversely, if the avatar appears above the stimulus, the approach and avoidance movement are reversed – the top key is associated with an avoidance movement and the bottom key is associated with an approach movement.

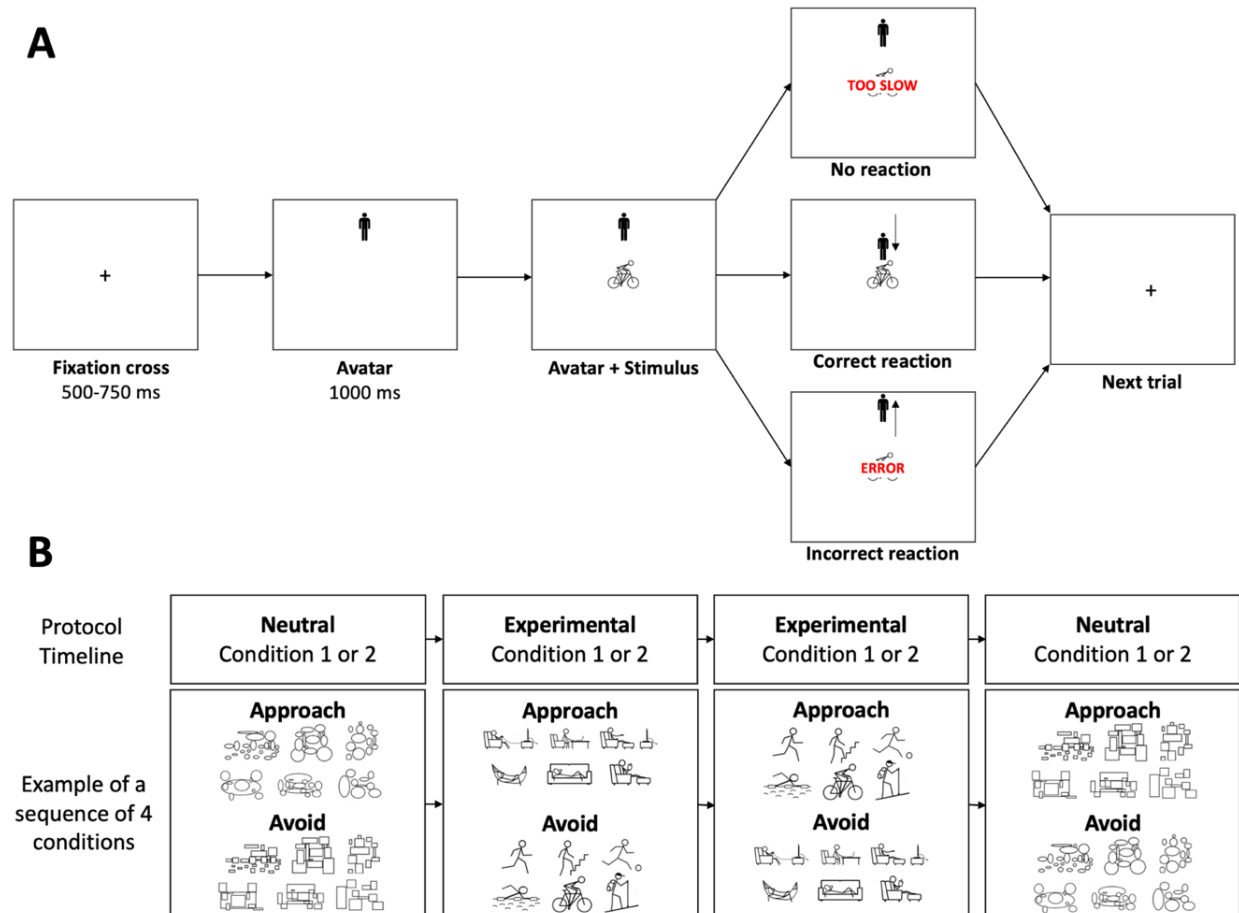


Figure 1. A. Illustration of a trial of the approach-avoidance task in the condition where the participant is instructed to approach physical activity stimuli (and avoid sedentary stimuli – not shown). B. Timeline and stimuli of the approach-avoidance task. In the experimental and neutral Condition 1, the participant is instructed to move the avatar toward (i.e., approach) a type of stimuli (i.e., physical activity or rectangles) and to move the avatar away from (i.e., avoid) stimuli depicting the other type of stimuli (i.e., sedentary behavior or ellipses, respectively). In Condition 2, the instruction is reversed: The participant is instructed to move away from physical activity (experimental condition) or rectangle stimuli (neutral condition) and move toward sedentary stimuli or ellipse stimuli.

Experimental Conditions

Two experimental conditions were tested ([Figure 1B](#)). In one experimental condition, the participant is instructed to quickly move the avatar toward (i.e., approach) pictograms depicting physical activity and to move the avatar away from (i.e., avoid) pictograms depicting sedentary behavior. In the other experimental condition, the participant does the opposite: move away from physical activity and move toward sedentary stimuli. The order of the experimental conditions was randomized across participants. In a previous study (Cheval, Tipura, et al., 2018), thirty-two participants were asked to rate the extent to which 24 stimuli expressed “movement and an active lifestyle” and “rest and sedentary lifestyle” (1= not at all, 7 = a lot). For each stimulus, the “rest and sedentary lifestyle” score was subtracted from the “movement and active lifestyle” score. In the current study, the six stimuli with the largest positive and negative differences were chosen as the stimuli depicting physical activity and sedentary behaviors, respectively.

Neutral Conditions

In addition to the two experimental conditions, two neutral conditions were tested. These conditions were used to account for a potential generic approach-avoidance tendency that could vary across participants and ages (Farajzadeh et al., 2023). In these neutral conditions, the stimuli depicting physical activity and sedentary behaviors were replaced by stimuli made of rectangles or ellipses that matched the number and size of information in 3 physical activity stimuli (swimming, hiking, cycling) and 3 sedentary stimuli (couch, hammock, reading). Two conditions were tested. In one condition, participants are asked to quickly move the manikin toward stimuli with circles and away from stimuli with squares. In the other condition, the participant is given opposite instructions. The order of the neutral conditions was randomized. One neutral condition

was tested before the two experimental conditions, and the other neutral condition was tested after them. Each condition included 96 stimuli, 48 of each class (physical activity and sedentary stimuli in the experimental conditions; rectangles and ellipses in the neutral conditions), that were presented randomly. Familiarization with the task was performed during the first 15 trials of the study, which were removed from the analyses. Familiarization with the subsequent conditions was performed during the first 3 trials of each condition, which were removed from the analyses. The physical activity and sedentary stimuli were presented all together on the screen for seven seconds before each experimental condition. Between conditions, the participant could rest for as long as they wanted before pressing the space key to start the next condition. When the participant pressed the incorrect key (“U” when it should be “N” or “N” when it should be “U”), the message “error” appeared on the screen for 800 ms before the next trial. When the reaction time (i.e., the time between the appearance of the stimuli and the key press) was longer than eight seconds, the message “too slow” appeared on the screen for 800 ms before the next trial ([Figure 1A](#)).

Reaction Times

The tendency to approach or avoid a type of stimuli (i.e., physical activity, sedentary, or neutral stimuli) was derived from the time required to press the key in reaction to a type of stimulus (i.e., physical activity vs. sedentary vs. neutral). Corrected reaction times were computed by subtracting the mean reaction time to approach or avoid neutral stimuli from the reaction time on each trial to respectively approach or avoid stimuli depicting a type of behavior (physical activity or sedentary behavior). The bias toward a type of stimulus (physical activity or sedentary behavior) was computed by subtracting the mean corrected reaction time to approach this type of stimulus from the corrected reaction time to avoid it. Therefore, positive scores were indicative of an approach bias, i.e., a higher tendency to approach the stimulus. Incorrect responses, responses

faster than 150 ms, and responses slower than 3,000 ms were excluded from the analyses to account for outliers and loss of attention (Farajzadeh et al., 2023). Specifically, because simple reaction times are typically longer than 200 ms (Fozard et al., 1994), and because we were assessing choice reaction times, we considered that reaction times faster than 150 ms could not be considered reactions to the stimuli of our task. In young adults, complex choice reaction times with up to 15 choices and different combinations of limb responses are typically faster than 1,000 ms (Boisgontier et al., 2014). However, in older adults, they can be longer than 3,000 ms (Boisgontier et al., 2016). Therefore, as with the lower threshold (150 ms), we chose a conservative upper threshold to avoid excluding a large proportion of valid reaction times in the older participants, as these observations can have a significant impact on the results (Miller, 2023; Ulrich & Miller, 1994). We did not include reaction times longer than 3000 ms because even in the complex task mentioned above (Boisgontier et al., 2016), the proportion of reaction times longer than 3,000 ms was less than 0.5% of the data. Therefore, we considered reaction times longer than 3,000 ms to be too long to be solely representative of a response to the stimuli of our task.

3.2.5. Statistical Analyses

To examine the mediation effect of intentions on the association between apathy and the habitual level of moderate-to-vigorous physical activity, we used the component approach (Yzerbyt et al., 2018). This component approach to the assessment of mediation was preferred over the index approach (Hayes, 2022), because the latter has shown a higher risk of false positives (Type I errors) (Yzerbyt et al., 2018). The component approach involves three linear multiple regressions models. Model 1 examines whether the independent variable affects the dependent variable. Model 2 examines the effect of the independent variable on the mediator. Model 3 examines both the independent variable and the mediators' simultaneous predictors of the

dependent variable. Mediation was claimed if the “total effect” of the dependent variable in Model 1 is larger in absolute value than its “residual effect” in Model 3. The bias to approach physical activity stimuli, the bias to approach sedentary stimuli, depressive symptoms, age, sex, body mass index, and the number of chronic health conditions were included as control variable in all the models used to test the mediation. The first mediation analysis examined the intention to be active as a mediator of the effect of apathy on the habitual level of physical activity. The second mediation analysis examined explicit attitudes as a mediator of the effect of apathy on the intention to be active. The third mediation analysis examined approach-avoidance tendencies as a mediator of the effect of apathy on the intention to be active.

To further examine the effect of apathy on approach-avoidance attitudes related toward physical activity and sedentary stimuli, a linear and a logistic mixed-effect models (Lohse et al., 2023) were built and fit by maximum likelihood in the R software environment (<https://www.r-project.org/>; Version 4.3.1), using the lme4 (Bates et al., 2015) and lmerTest package (Kuznetsova et al., 2017), which approximates p-values using Satterthwaite’s degrees of freedom method. Continuous variables were standardized. For the linear mixed-effects model, restricted maximum likelihood (REML) was used as it provides less biased estimates of variance components than full maximum likelihood (Luke, 2016). Fixed effects included a three-way interaction effect of apathy (continuous), stimulus (physical activity vs. sedentary behavior), and action direction (approach vs. avoid) on corrected reaction time. The other fixed effects controlled for the effect of depressive symptoms, the habitual level of moderate-to-vigorous physical activity, age, sex, body mass index, the number of chronic conditions, and the device used to complete the study (computer vs. tablet). Our balanced design was fully crossed: Each participant was tested in the approach and avoid condition of four types of stimuli (physical activity, sedentary behavior, rectangles, ellipses), with

each type including 6 pictograms. Therefore, we intended to include the random effect of participant, action direction, stimulus, and pictogram (Lohse et al., 2023). However, the model converged only when the random effects of stimulus was removed.

To ensure that the results obtained with the corrected reaction times cannot be explained by the speed-accuracy trade-off (Hick, 1952), we conducted a logistic mixed-effects model with the number of errors in the approach-avoidance task as outcome. The structure of this model was similar to the linear mixed-effects models using reaction time as outcome. However, because the logistic mixed-effects models did not converge when the three-way interaction was included, we conducted a model with a two-way interaction between apathy and action direction on errors when reacting to physical activity stimuli and another model with the same interaction but in the conditions with sedentary stimuli. In addition, only the fixed effects of depressive symptoms, age, and explicit attitudes as well as the random effect of participant were included to allow for model convergence.

3.3. Results

3.3.1. Descriptive Results

3.3.1.1. Participants

Three hundred and ninety-two participants initiated the study. Some of them were included in a previous study from our group (Farajzadeh et al., 2023). Twenty-three were excluded because they stopped the session before completing the study. Four participants were excluded because they answered the check question incorrectly. When participants reported height < 50 cm or > 250 cm or weight < 30 kg or > 250 kg, the data was removed and imputed using the sample mean. The final sample of 365 participants was 53.7 ± 17.9 years (mean $\pm$ standard deviation), with a mean score of behavioral apathy of 31.3 ± 9.3 out of a maximum of 77 (mean score per item of 2.9 ± 0.9

on a scale ranging from 1 to 7), a habitual level of moderate-to-vigorous physical activity of 398.3 ± 496.0 min per week, mean depressive symptoms of 0.7 ± 0.4 , body mass index of 27.6 ± 12.1 kg.m-2, and 1.5 ± 1.5 chronic health conditions. Two males identified themselves as women. All the other male (n = 146) and female participants (n = 217) identified themselves as men and women, respectively.

Table 1 – Descriptive statistics (n = 365, 148 females)

Variable (minimum score-maximum score)	Mean	SD	Range
Age (years)	53.7	17.9	20-89
Body mass index (kg.m ⁻²)	27.6	12.1	15.1-48.7
Moderate-to-vigorous physical activity (min.week ⁻¹)	398.4	496.0	0-3080
Explicit Attitude (2-14)	11.0	3.2	2-14
Intention (1-7)	5.1	2.1	1-7
Behavioral Apathy (11-77)	31.3	9.3	11-60
Depression (0-48)	9.3	6.2	0-37
Chronic Diseases (0-18)	1.5	0	7
Approach physical activity stimuli (ms)	1094	547	163-2996
Avoid physical activity stimuli (ms)	1183	538	172-2998
Approach sedentary stimuli(ms)	1202	590	174-2996
Avoid sedentary stimuli (ms)	1153	535	192-2989
Approach neutral stimuli (ms)	1021	542	156-2999
Avoid neutral stimuli (ms)	1046	523	154-2997

3.3.1.2. Cut-Off Score for Behavioral Apathy

In our study, 126 participants reported having no chronic condition. In this subsample, the mean score per item was 2.93 on a scale of 1 to 7, with a 95% confidence interval (95CI) ranging from 2.79 to 3.07. This result suggested that a mean score per item $> 34.5\% [(3.07 - 1) / (7 - 1)]$ of the scale range is indicative of behavioral apathy. Based on this cut-off score, participants with a score ≥ 34 would be classified as adults with apathy (i.e., 37.5% of the participants). The same

approach applied to our full sample (n = 365) yielded similar results (95CI upper bound = 2.98; 33.1% of the scale range).

3.3.1.3. Observations in the Approach-Avoidance Task

A total of 71,378 trials were performed by the participants ([Figure 2](#)), of which 12,350 were excluded: 531 trials were aborted at eight seconds with the “too slow” message appearing on the screen, 768 were removed because the participants failed the attention check question, 3,965 reactions were longer than 3,000 ms and 119 were faster than 150 ms, and 6,967 were familiarization trials. Among the 59,028 trials included in the analyses, 55,050 were in the correct direction (14,523 for sedentary stimuli and 14,724 for physical activity stimuli, 25,803 for neutral stimuli). An error occurred in 3,978 trials. A total of 15,539 trials were reactions to sedentary stimuli and 15,662 to physical activity stimuli (including reactions in the correct and incorrect direction).

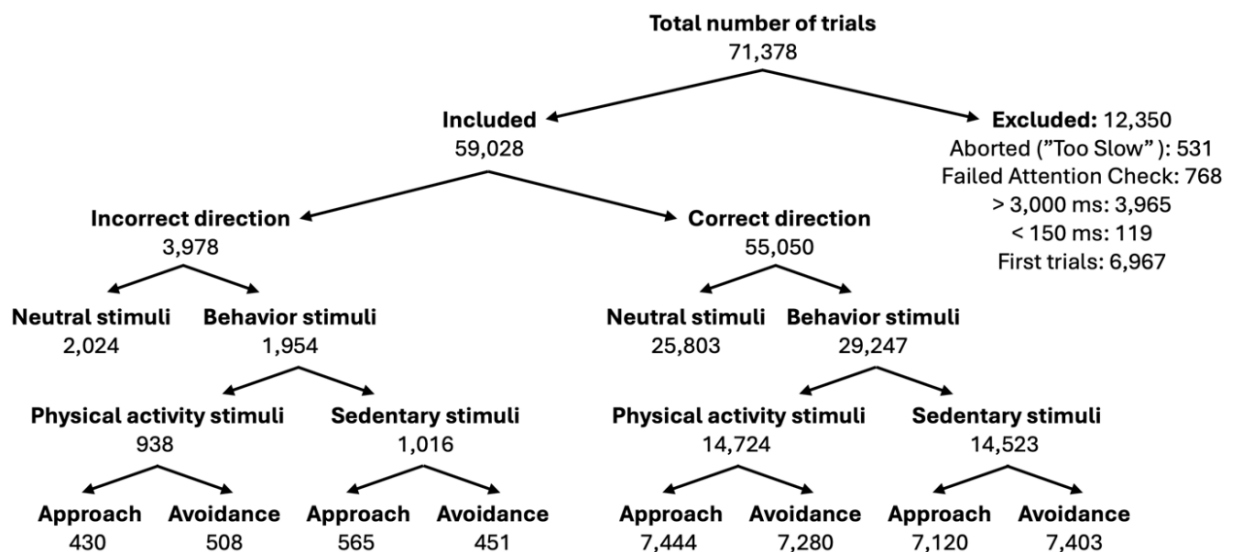


Figure 2. Flow diagram depicting the distribution of the trials

3.3.2. Statistical Results

3.3.2.1. Intentions Mediate the Effect of Apathy on Physical Activity Engagement

Model 1 showed an association between apathy and the habitual level of physical activity ($b = -67.6$; 95CI = -119.1 to -16.2; $p = .010$). Model 2 showed an association between apathy and the intention to be physically active ($b = -0.220$; 95CI = -0.431 to -0.009; $p = .041$). Model 3 showed an association between intentions and physical activity ($b = 147.3$; 95CI = 97.4 to 197.3; $p = 1.48 \times 10^{-8}$). Model 3 also showed that the association between apathy and the level of physical activity was reduced when intentions were added as a predictor ($b = -51.9$; 95CI = -101.4 to -2.3; $p = .040$). From model 1 to 3, this association decreased by 23.3%. Taken together, these results demonstrate that the intention to be physically active partially mediates the relationship between apathy and the habitual level of physical activity ([Figure 3](#)).

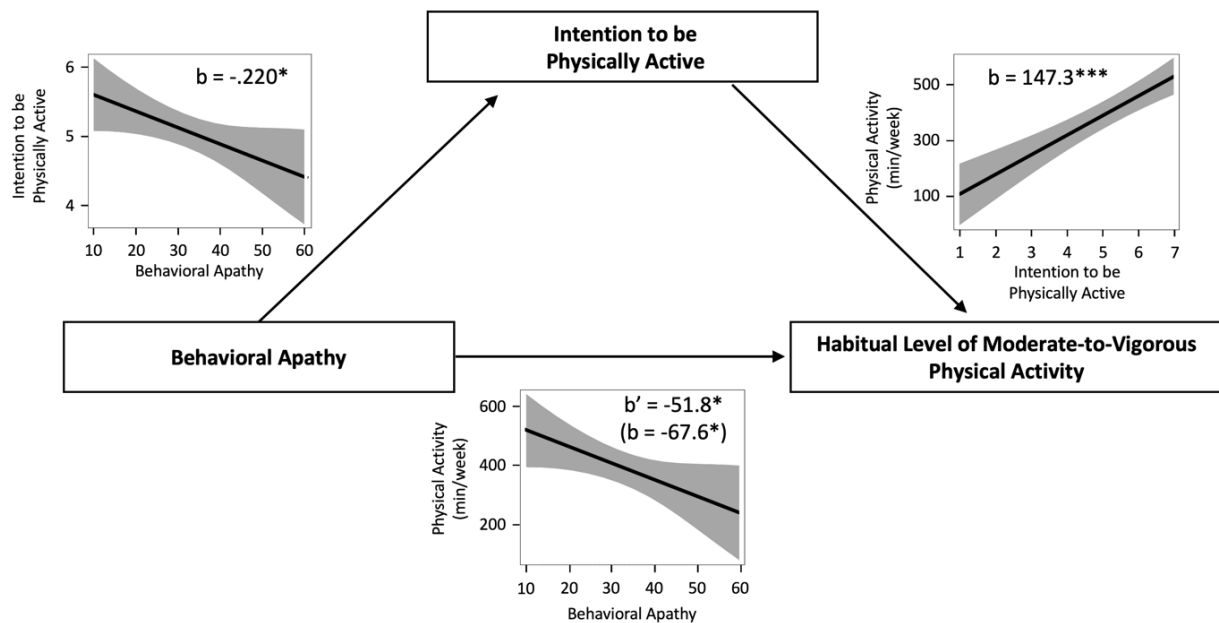


Figure 3. Mediation effect of intention to be physically active on the association between apathy and the habitual level of physical activity.

Note: b' is the estimate of the residual effect of apathy when intention is included in the model

3.3.2.2. Explicit Attitudes Mediate the Effect of Apathy on Intentions

Model 1 showed an association between apathy and the intention to be physically active ($b = -0.220$; $95\text{CI} = -0.431$ to -0.009 ; $p = .041$). Model 2 showed an association between apathy and explicit attitudes toward physical activity ($b = -0.707$; $95\text{CI} = -1.019$ to -0.394 ; $p = 1.15 \times 10^{-5}$). Model 3 showed an association between explicit attitudes and the intention to physically active ($b = 1.376$; $95\text{CI} = 1.202$ to 1.550 ; $p < 2 \times 10^{-16}$). Model 3 also showed that the association between apathy and intentions to be physically active was no longer significant when explicit attitudes were added as a predictor ($b = 0.084$; $95\text{CI} = -0.083$ to 0.252 ; $p = .324$). Taken together, these results demonstrate that explicit attitudes fully mediate the relationship between apathy and intentions to be physically active (Figure 4).

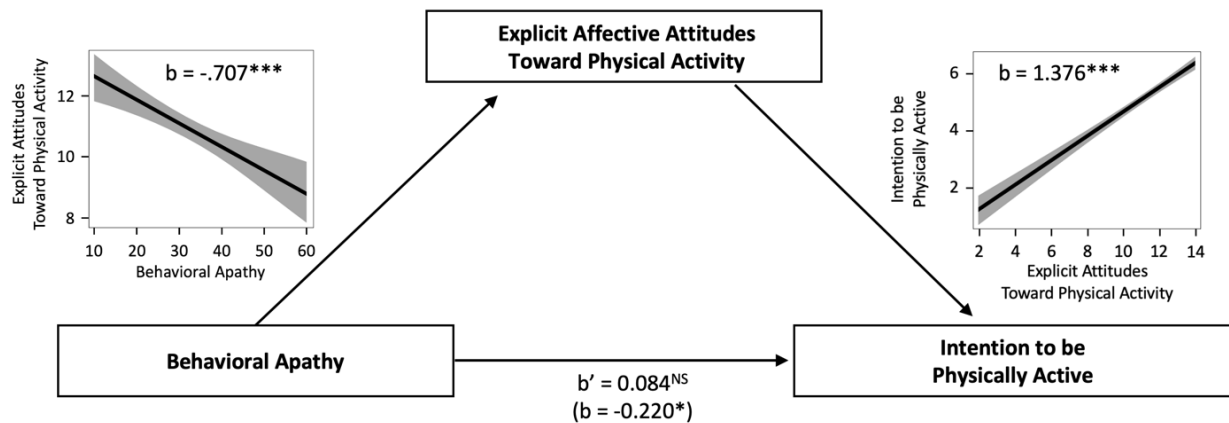


Figure 4. Mediation effect of explicit affective attitudes on the association between apathy and intentions to be physically active

Note: b' is the estimate of the residual effect of apathy when explicit affective attitudes are included in the model

3.3.2.3. Apathy and Approach-Avoidance Tendencies

Results of the linear mixed-effects model showed a significant three-way interaction between apathy(continuous), stimulus (physical activity vs. sedentary behavior), and action direction (approach vs. avoid) on corrected reaction time ($b = 19.6$; $95\text{CI} = 2.0$ to 37.3 ; $p = .029$)

(Figure 5). Simple effect analyses showed that lower apathy scores were associated with faster approach than avoidance of physical activity stimuli, but this difference was no longer significant when the apathy score was ≥ 55 out of a maximum mean score of 77. In addition, simple effect analyses showed that lower apathy scores were associated with faster avoidance than approach of sedentary stimuli, but this difference was no longer significant when the apathy scores were ≥ 70 . In other words, lower apathy was associated with tendencies to approach physical activity stimuli and to avoid sedentary stimuli. Both these tendencies suggested a positive automatic evaluation of stimuli associated with physical activity. However, such tendencies decreased as apathy increased until they lost their statistical significance. Results of the logistic mixed-effects models showed no evidence of an interaction between the effects of apathy and action direction on errors when reacting to physical activity ($b = .135$; $95\text{CI} = -.011 \text{ to } .283$; $p = .07$) or sedentary stimuli ($b = .128$; $95\text{CI} = -.025 \text{ to } .283$; $p = .103$). Additionally, results showed no evidence of an association between approach-avoidance tendencies and the habitual level of moderate-to-vigorous physical activity, ruling out the possibility for a mediation effect.

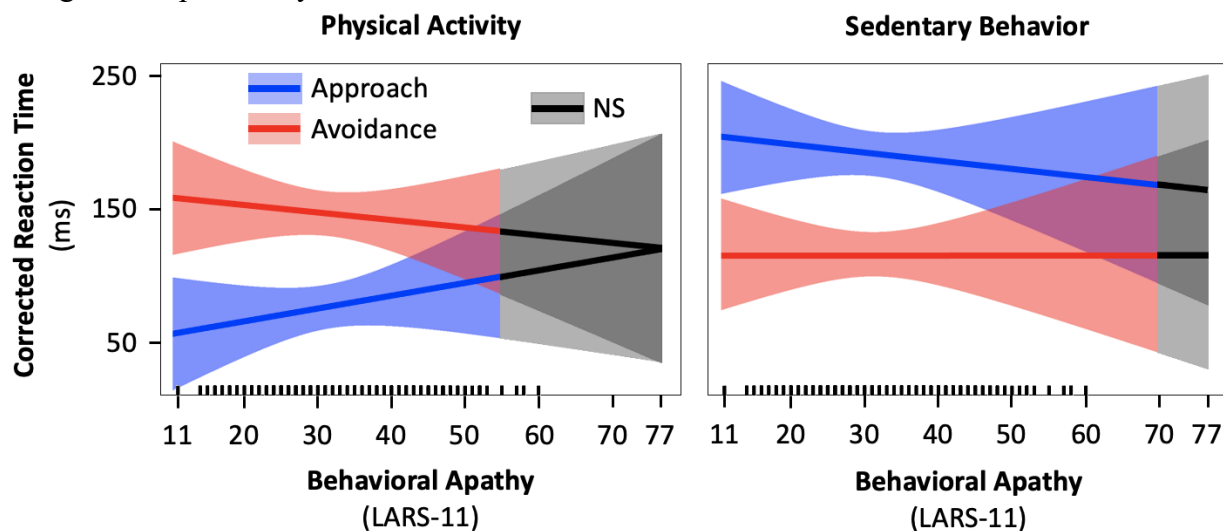


Figure 5. Results of the three-way interaction between the effect of apathy (continuous), stimulus (physical activity vs. sedentary behavior), and action direction (approach vs. avoid) on corrected reaction time.

Note. LARS = Lille Apathy Rating Scale. NS = Non significant effect of action direction.

3.4. Discussion

3.4.1. Main Findings

As hypothesized, weaker intention to be physically active mediated the association between higher behavioral apathy and lower habitual levels of moderate-to-vigorous physical activity. In addition, explicit attitudes mediated the relationship between behavioral apathy and intentions to be physically active. While higher apathy was associated with a stronger tendency to avoid physical activity stimuli and to approach sedentary stimuli, we found no evidence suggesting that this tendency mediated the relationship between apathy and intentions or habitual physical activity. Based on our data, a mean item score greater than 34.5% of the scale range (e.g., >3.07 on a 1–7 scale) is indicative of behavioral apathy.

3.4.2. Comparison with the Literature

3.4.2.1. Behavioral Apathy Cut-Off Score

Our data in otherwise healthy older adults ($n = 126$) suggest that a mean score per item > 34.5% of the scale range is indicative of behavioral apathy. Based on this cut-off score, 37.5% of our participants ($n = 365$) would be classified as having behavioral apathy. Of note, this cut-off score was similar to the one based on our entire sample (33.1% of the scale range), which is consistent with the absence of statistical correlation between behavioral apathy and chronic conditions ($r = -0.017$, $p = .742$) and with the conceptualization of apathy as a syndrome rather than a symptom, since apathy levels were similar regardless of health status. In addition, our cut-off score is consistent with the mean item score of 29.7% of the scale range that was used as a cut-off score in another study of otherwise healthy young and middle-aged adults ($n = 108$, 94.5%

aged 20 to 49 years), although they used a different scale, the Apathy Evaluation Scale ranging, which ranges from 1 to 4 (Kant et al., 1998). However, other results in otherwise healthy young adults ($n = 139$) showed a mean apathy score per item of 1.46 on a scale of 1 to 5, with an upper bound 95CI of 1.58 (Bonnelle, Manohar, et al., 2016). Accordingly, they considered a mean score per item of 14.5% of the scale range to reflect behavioral apathy. Based on this cut-off score, 88.5% of our sample would have been classified as adults with apathy. We initially hypothesized that this higher threshold for apathy in our study compared to the study by Bonnelle et al., (2015) might be due to the broader age distribution (mean age: 27.4 ± 7.8 vs. 53.7 ± 17.9 years) since a recent meta-analysis showed stronger correlation between apathy and physical activity in older adults compared to younger adults (Farajzadeh et al., 2024). However, our results showed no evidence of a positive correlation between behavioral apathy and age in the healthy subset ($r = -0.173$, $p = .053$).

3.4.2.2. Behavioral Apathy and Physical Activity

The association between apathy and physical activity observed in the current study aligns with results of a recent meta-analysis, which reported a negative correlation based on 22 studies ($n = 12,541$) (Farajzadeh et al., 2024).

3.4.2.3. Mediating Role of Intentions

For the first time, we show an association between behavioral apathy and intentions to be physically active. This finding suggests that behavioral apathy affects the intention stage of goal-directed behaviors (Levy & Dubois, 2006), such as physical activity. In addition, this finding is conceptually coherent because behavioral apathy, a motivational impairment (Levy & Dubois, 2006; Marin, 1990; Marin, 1991), is likely to reduce the amount of effort individuals are willing to invest for the physical activity behavior to occur. This reduction could be explained by an

increased sensitivity to effort (Bonnelle et al., 2015) and/or a reduced sensitivity to rewards associated with physical activity (Pessiglione et al., 2017), both of which could be linked to changes in brain circuitry, even at subclinical levels of apathy (Derosiere et al., 2024). Our results also show an association between the intention to be physically active and the engagement in physical activity behavior, which is in line with previous theoretical and experimental literature (Ajzen, 1987; Biddle et al., 2007; Maltagliati, Raichlen, et al., 2024). Recent experimental results based on the theory of effort minimization in physical activity (Cheval & Boisgontier, 2021; 2024) suggest that this association between intentions and physical activity behavior is influenced by individual differences in the general tendencies to approach and avoid physical effort (Cheval & Boisgontier, 2024; Maltagliati, Raichlen, et al., 2024). Specifically, the positive association between intentions to be physically active and physical activity engagement was stronger when self-reported tendencies to approach physical effort were higher, and weaker when tendencies to avoid physical effort were higher. These findings encourage future studies to examine whether approach-avoidance tendencies toward physical effort influence the relationship between behavioral apathy and physical activity engagement. The observed mediating effect of intention suggests that interventions aimed at increasing physical activity levels in patients with apathy should first focus on enhancing their intention to be physically active. While such intention does not guarantee engagement in physical activity, it is an essential prerequisite for this engagement (Feil et al., 2023; Rhodes & de Bruijn, 2013).

3.4.2.4. Mediating Role of Explicit Attitudes

For the first time, we show an association between behavioral apathy levels and explicit affective attitudes toward physical activity, which mediate the relationship between apathy and intentions to be physically active. These attitudes are based on the aggregation of the likelihood of

anticipated affective responses (Stevens et al., 2020; Williams & Evans, 2014). Therefore, to strengthen positive explicit attitudes in individuals with apathy, ensuring that exercise therapy is consistently associated with positive experiences may be important. This suggestion is consistent with existing literature highlighting the role of pleasure and displeasure in physical activity engagement (Ekkekakis, 2017; Maltagliati, Sarrazin, et al., 2024). Ultimately, this effect of explicit attitudes on intentions may influence behavior as within-subject increases in positive affect have been shown to be associated with physical activity levels at 3-month follow-up (Kwan & Bryan, 2010).

3.4.2.5. Physical Activity and Approach-Avoidance Tendencies

Literature has consistently reported a tendency to approach physical activity stimuli and to avoid sedentary stimuli at all ages (Farajzadeh et al., 2023). In the current study, we showed that these tendencies are influenced by apathy. Participants with stronger behavioral apathy showed weaker tendencies to approach physical activity and avoid sedentary behaviors. Approach-avoidance tendencies reflect motivational processes that direct organisms toward beneficial stimuli (approach) and away from detrimental stimuli (avoidance), driving adaptive behavior (Elliot et al., 2013). These tendencies are driven by internal states and action plans that translate perceived urges into behavior (Sander et al., 2018). Specifically, factors such as the perceived reward and the amount of effort involved in a behavior can influence whether a person is motivated to approach or avoid this behavior. Apathy, characterized by reduced motivation and difficulty generating action plans for goal-directed behavior, results from a desensitization to reward (Martínez-Horta et al., 2014; Muhammed et al., 2016) or an increased sensitivity to effort (Bonnelle et al., 2015; Le Heron et al., 2018; Le Heron et al., 2018). Therefore, individuals with apathy may perceive physical activity as more effortful and less rewarding than individuals without apathy. Thus, the

threshold of the reward-to-effort ratio that triggers behavior may be harder to reach, reducing the likelihood of approaching physical activity. This example illustrates how apathy can disrupt the approach-avoidance dynamic and dampen the internal drive toward physical activity behavior.

3.4.3. Limitations and Strengths

The present study has potential limitations. First, the online nature of the study made it impossible to limit the influence of potential distractions in the participant's environment and to control whether participants were using their two index fingers to perform the task as instructed and whether they were sitting or standing, which could have influenced the results (Cheval, Radel, et al., 2018; Maltagliati, ten Broeke, et al., 2024). Second, the participants were recruited in Canada. It is, thus, unclear whether conclusions could generalize to populations from non-Western countries or less active populations of older adults. Third, the habitual level of physical activity was assessed using a self-reported questionnaire, which may not accurately reflect the objective level of physical activity. Assessing physical activity and sedentary behaviors using device-based measures would have provided more reliable estimates. However, these limitations are offset by several strengths, including a large sample size, a measure that accounts for a potential generic approach-avoidance bias that could have confounded the results (Farajzadeh et al., 2023), and the use of statistics that limit information loss (i.e., mixed effects models) (Boisgontier & Cheval, 2016; Lohse et al., 2023).

3.5. Conclusion

This study supports previous work suggesting that apathy is a syndrome rather than a symptom (Marin, 1991), affecting not only individuals with a medical condition but also otherwise healthy adults across all ages. In addition, the results highlight the key role of intentions and explicit affective attitudes in mediating the relationship between behavioral apathy and habitual

physical activity. These insights suggest that interventions aimed at improving or maintaining physical activity levels should assess apathy regardless of a patient's or client's health status. For individuals identified as having apathy, incorporating motivational constructs—such as the intention to be physically active and positive affective attitudes toward physical activity—into the intervention design should be considered.

3.6. Data Availability

According to good research practices (Boisgontier, 2022), the dataset and the R script are available in Zenodo (Boisgontier, 2024) which can be found at <https://doi.org/10.5281/zenodo.12750404>.

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Chapter 4

Physical Activity and Motor Cortex Neurophysiology: A Systematic Review and Meta-Analysis of Transcranial Magnetic Stimulation Measures of Excitability, Inhibition, and Facilitation.

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4.1. Introduction

The primary motor cortex (M1) plays a key role in the control of voluntary movement by integrating inputs from multiple cortical and subcortical regions and transforming them into descending corticospinal signals that drive skeletal muscle activity¹. In the short term, corticospinal excitability is dynamically modulated during action preparation and selection, reflecting the influence of distributed neural circuits involved in action control². Beyond these short-term modulations, M1 circuits exhibit plasticity and can be modified through experience and motor practice³.

Physical activity, which includes exercise, sport, active transport, household chores, and occupational activities⁴, may influence M1 plasticity. Evidence from systematic reviews and meta-analyses indicates that acute exercise can modulate several measures of motor cortical function, including corticospinal excitability as well as intracortical inhibitory and facilitatory circuits^{5, 6}. These acute effects, typically observed within minutes to hours following exercise, may be mediated by transient neurochemical changes, including increases in circulating catecholamines and neurotrophic factors^{7, 8}. Whether the repeated occurrence of such acute effects through regular engagement in physical activity results in longer-term differences in M1 neurophysiology remains unclear.

Although the association between habitual physical activity, reflecting typical levels of physical activity accumulated across daily life⁴, and M1 neurophysiology has not been systematically reviewed, several lines of evidence suggest that such a relationship may exist. Habitual physical activity has been associated with alterations in neural systems supporting plasticity, including increases in circulating neurotrophic factors such as brain-derived neurotrophic factor⁹. Moreover, motor cortical responses to acute exercise appear to depend on

habitual physical activity levels, suggesting that individual differences in physical activity may influence M1 neurophysiology^{10, 11}.

In humans, M1 neurophysiology can be probed non-invasively using transcranial magnetic stimulation (TMS). Single-pulse TMS allows assessment of corticospinal excitability (CSE) through motor-evoked potentials (MEPs), whereas paired-pulse TMS protocols probe inhibitory and facilitatory cortical circuits, including short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), intracortical facilitation (ICF), and short-interval intracortical facilitation (SICF)^{12,13}. In addition, TMS can assess inhibitory processes using measures such as the cortical silent period (cSP) and the ipsilateral silent period (iSP), which reflect cortical and interhemispheric inhibition, respectively¹⁴. Despite growing interest in the neurobiological effects of physical activity, the relationship between habitual physical activity and these TMS-derived measures of M1 neurophysiology has not been systematically reviewed. Therefore, the aim of this study was to conduct a systematic review and meta-analysis examining the association between habitual physical activity and TMS-derived measures of motor neurophysiology.

4.2. Methods

4.2.1. Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁵. Potentially eligible studies were identified through systematic searches of MEDLINE (via PubMed), PsycINFO, Web of Science, SPORTDiscus, and CINAHL. The search strategy combined terms related to physical activity (e.g., physical activity, physical education, training, physical fitness, exercise, cycling, treadmill, single bout) and TMS (e.g., TMS, transcranial magnetic stimulation, motor-evoked

potential, stimulus-response curve, input-output curve, intracortical inhibition, intracortical facilitation, silent period) (see Suppl. Material 1 for the full search strategy). The search included all articles published in English available from inception up to March 2025, with no limitation on the start date. In addition, the reference lists of included articles were manually screened to identify potentially relevant studies not captured in the database searches. An updated search was conducted covering the period from April 2025 to February 2026. To reduce potential bias and enhance transparency, this systematic review was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251016029) and approved by the Office of Research Ethics and Integrity at the University of Ottawa (H-03-26-12745).

4.2.2. Eligibility Criteria

Studies were included if they were published in a peer-reviewed journal, were written in English, reported original data collected from healthy adult participants (≥ 18 years), included at least one neurophysiological measure of M1 assessed using TMS and at least one measure of physical activity, and formally tested the association between these variables (e.g., by reporting a Pearson's r correlation coefficient). Measures of physical activity could be self-reported (e.g., questionnaire) or device-based (e.g., accelerometry). Eligible study designs included cross-sectional studies, cohort studies, and baseline data from clinical trials. Studies were excluded if they were published as a review article, book chapter, study protocol, or conference abstract, or assessed laboratory-based measures of physical fitness (e.g., maximal muscle force).

4.2.3. Study Selection

One author (AF) conducted the initial database search. After removing duplicates, the titles and abstracts of all identified records were screened according to the predefined inclusion and

exclusion criteria. Studies that did not meet the eligibility criteria were excluded. In the second stage, two authors (AF, KP) independently screened the full text of the remaining articles. Both reviewers had to agree on the inclusion or exclusion of each study. Any disagreements were resolved through discussion and consensus, with a third reviewer (MPB) consulted when necessary. Reference list screening and forward citation tracking were conducted for all studies retained after the full-text screening stage ([Figure 1](#)).

4.2.4. Data Extraction

Data extraction was performed independently by two reviewers (AF, KP). Any discrepancies were resolved through discussion and consensus, with a third reviewer (MPB) consulted when necessary. When insufficient data were reported, the corresponding author was contacted to request additional information. Data were extracted from the included studies using a standardized extraction form. The extracted information included the first author's name, article title, publication year, study design, sample size, age range, mean age, sex distribution, type of physical activity measure, duration of physical activity assessment, outcome measures, TMS measures, and results describing the association between physical activity and neurophysiological measures. These measures included MEP amplitude (reflecting CSE); expressed as raw amplitude, percentage of peripheral M-wave amplitude, MEPMAX, or values derived from a stimulus–response curve, as well as SICI, LICI, cSP, iSP, ICF, and SICF. When studies met all inclusion criteria but did not report the association of interest, the corresponding author was contacted by email to request the relevant information.

4.2.5. Quality Assessment

The methodological quality of each included study was assessed using the Downs and Black checklist¹⁶. This checklist can be applied to both randomized and non-randomized studies

and consists of 27 items assessing reporting quality, external validity, internal validity, and statistical power. Total scores range from 0 to 28, with higher scores indicating better methodological quality. Two reviewers (AF, KP) independently assessed study quality, and discrepancies were resolved through discussion and consensus with a third reviewer (MPB).

4.2.6. Statistical Analyses

All analyses were conducted with R software¹⁷ in RStudio statistical environment using metafor¹⁸ and meta packages¹⁹. When correlations were directly reported, these values were extracted. When correlations were not reported, they were computed from available statistics (e.g., t-values, exact p-values, and sample sizes) using custom R scripts (Suppl. Material 2) based on standard relationships between test statistics and correlation coefficients. To ensure consistent interpretation across inhibitory measures, values were examined and, where necessary, recoded so that higher values consistently reflected stronger cortical inhibition. Correlations for SICI and LICI were then multiplied by -1 so that higher values consistently reflected stronger cortical inhibition across all measures.

4.2.6.1. Primary Meta-Analyses

Pearson product-moment correlations from eligible studies were pooled to examine the relationship between physical activity and TMS measures of cortico-spinal excitability, cortical inhibition, and cortical facilitation. Prior to analysis, r correlations were Fisher's z -transformed to stabilize variance, and the corresponding sampling variances were calculated.

Meta-analyses were conducted using multilevel random-effects models implemented with the metafor package¹⁸. This approach accounts for statistical dependence among multiple correlation estimates reported within the same study. A multilevel approach was used because several studies contributed more than one correlation estimate (e.g., different TMS outcomes or

measurement conditions), which introduces statistical dependence among effect sizes. Multilevel meta-analysis appropriately accounts for this dependency without requiring aggregation of effect sizes within studies. Specifically, correlation estimates were nested within studies, resulting in a three-level model (level 1: sampling variance, level 2: correlation estimates within studies, level 3: studies). Between-study heterogeneity was estimated using the restricted maximum likelihood estimator²⁰. Heterogeneity was quantified using the I^2 statistic, which represents the proportion of total variability in observed effect sizes that is not attributable to sampling error²¹. Because a multilevel meta-analytic model was used, I^2 values were decomposed across variance components to estimate the proportion of variability attributable to differences between studies and between effect sizes within studies.

To reduce the risk of inflated type I error rates, confidence intervals for pooled estimates were calculated using a Knapp–Hartung adjustment²². In addition to pooled correlations and their confidence intervals, prediction intervals were calculated to estimate the range within which the true effect size of a future study is expected to fall based on the current evidence. Unlike confidence intervals, which describe the precision of the pooled estimate, prediction intervals incorporate between-study heterogeneity to reflect the expected variability of effects across future studies. For visualization purposes, forest plots were produced using the meta package¹⁹ with a RevMan layout. These plots were based on random-effects models equivalent to the multilevel analyses.

4.2.6.2. Subgroup Meta-Analyses

Subgroup analyses were conducted to examine whether pooled correlations differed across types of inhibitory (SICI, LICI, cSP, and iSP) and facilitatory measures (ICF and SICF), as well as by physical activity assessment method (self-reported vs. device-based).

4.2.6.3. Meta-Regressions

Meta-regression analyses were conducted to examine whether study-level characteristics, including mean age and proportion of women were associated with the reported correlations.

4.2.6.4. Sensitivity Analysis

A sensitivity analysis was conducted to examine whether the quality of the studies affected the results.

4.2.6.5. Publication Bias

Potential publication bias and small-study effects were assessed using contour-enhanced funnel plots and Egger's regression tests. Funnel plots display the Fisher's z-transformed correlations against their standard errors to allow visual inspection of asymmetry around the pooled effect size. Egger's regression test was used as a statistical complement to the visual inspection of funnel plots. Because no direct implementation exists for multilevel meta-analytic models, the test was conducted using a meta-regression approach in which the standard error of the effect size estimate was included as a predictor in the multilevel model²³.

4.2.6.6. Equivalence Testing

When the results of the meta-analysis were not statistically significant, equivalence testing was conducted using the two one-sided tests procedure implemented in the TOSTER package²⁴ to determine whether pooled correlations were statistically equivalent to zero within prespecified equivalence bounds. Because no theoretically justified smallest effect size of interest could be identified, equivalence tests were conducted using bounds corresponding to a small correlation ($r = \pm 0.10$)²⁵. These bounds were converted to Fisher's z to match the metric used in the meta-analysis. The pooled correlation was considered statistically equivalent to zero and practically

negligible when the 90% confidence interval of the pooled effect fell entirely within the equivalence bounds.

4.3. Results

4.3.1. Literature Search

The primary search identified 4,511 potentially relevant articles across five databases ([Figure 1](#)), including 1,583 duplicates. After duplicate removal, 2,928 articles were screened, of which 2,736 were excluded for being unrelated to TMS or physical activity. The remaining 192 articles underwent full-text screening, resulting in 51 studies meeting the criteria for further investigation and potential inclusion. None of these studies reported a correlation coefficient between physical activity and TMS measures. We were able to estimate the correlation coefficient in five studies based on open data¹¹ or reported statistics^{10, 26–28}. We contacted the corresponding authors of the remaining 46 studies to request either the correlation estimate or the raw data required to compute it. At least one reminder email was sent when no response was received. Twenty-Four authors responded: two provided correlation coefficients^{29, 30}, Twelve provided raw data^{31–42}, three reported no longer having access to the data, and seven indicated they would follow up, but the requested information was not subsequently received. One study was excluded because it relied on the same dataset as another included study³⁷. Reference list screening and forward citation tracking identified two additional studies, none of whose authors responded to our emails. One additional dataset from our laboratory was included⁴³. Ultimately, out of the 53 studies meeting the criteria, 20 were included in the systematic review (37%). Detailed reasons for exclusion at each stage are provided in the PRISMA flow diagram ([Figure 1](#)). The methodological quality scores of the included studies ranged from 11 to 18 out of 28 (mean $\pm$ standard deviation of 13.7 ± 1.9) (Table 1).

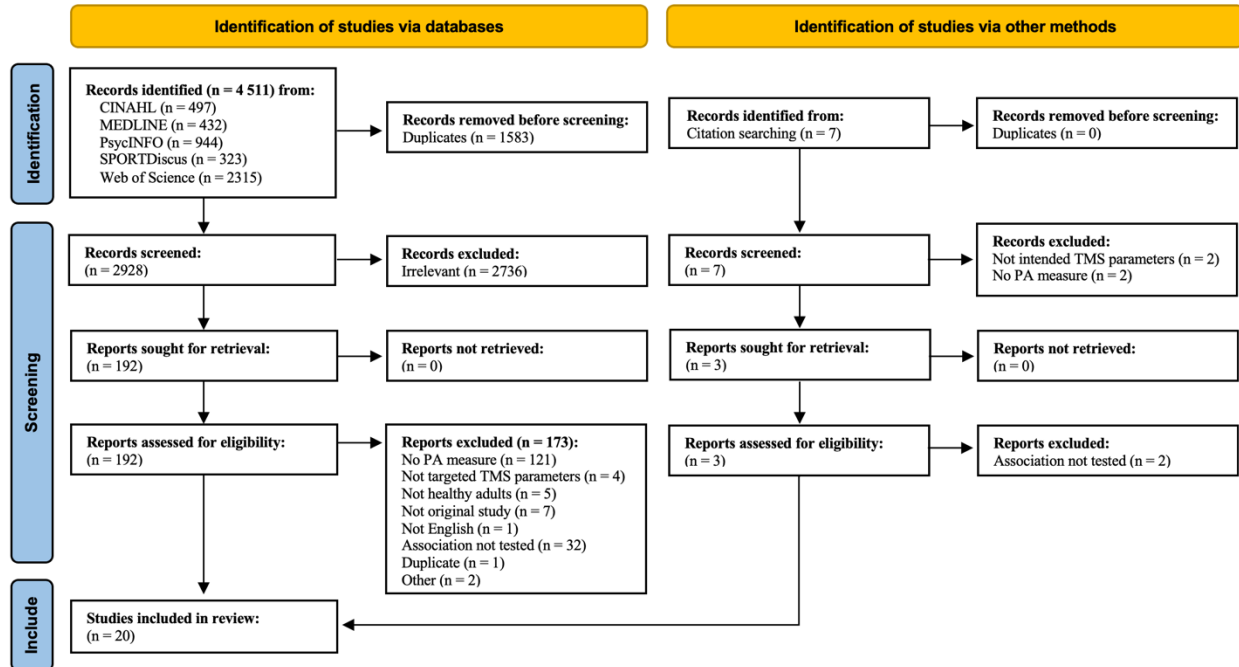


Figure 1. PRISMA flow diagram of study selection

4.3.2. Descriptive Results

4.3.2.1. Participants

The 20 articles included in the systematic review comprised 761 participants aged 19-78 years (404 males and 357 females), all of whom were healthy adults. Twelve studies included only young adults^{10, 11, 28, 32, 34–36, 38–41, 43}, three included only older adults^{29, 30, 42}, four included both young and older adults^{26, 31, 33, 37}, and one study included young and middle-aged adults²⁷.

4.3.2.2. Physical Activity

Four studies assessed physical activity using triaxial accelerometers^{30, 31, 33, 40}, which were worn at the waist (ActiGraph GT3X)^{31, 33, 43} or the wrist (ActivInsights GENEActiv)³⁰ (Table 1). Sixteen studies assessed physical activity using self-reported measures. Twelve of these used the International Physical Activity Questionnaire^{10, 11, 28, 32, 34, 35, 37–42}. Other self-report instruments were the Leisure Time Exercise Questionnaire²⁶, the Physical Activity Questionnaire³⁶, and ad-hoc

questionnaires^{27,29}. Physical activity outcomes included questionnaire scores from a questionnaire²⁶, MET-min/week^{10, 11, 28, 32, 34, 35, 37–42}, steps per day^{31, 33, 43}, and active time per week^{27, 29, 30, 36}.

4.3.2.3. Neurophysiological Measures

Seventeen studies assessed TMS measures in upper-extremity muscles^{10, 11, 26, 27, 29, 30, 32–38, 40–43}. Two studies examined both upper- and lower-extremity muscles^{28, 39}, and one examined only lower-extremity muscles³¹. CSE was assessed in fifteen studies^{10, 11, 29–36, 38–41, 43}. SICI was assessed in eleven studies, using an interstimulus interval (ISI) of 2 ms^{10, 11, 28, 32, 35, 36, 40, 41, 43}, 2.5 ms³⁴, or 3 ms⁴⁰. LICI was assessed in one study using an ISI of 100 ms⁴³. cSP was assessed in two studies^{10, 29} and iSP in two studies^{26, 27}. ICF was assessed in seven studies, with ISI of 10 ms in four studies^{11, 28, 35, 36} and 12 ms in three studies^{34, 37, 43}. SICF was assessed in three studies using ISIs of 1.2 ms¹¹, 1.5 ms^{28, 35}, and 2.5 ms¹¹.

4.3.2.4. Association Between Physical Activity and Neurophysiological Measures

Two authors provided correlation coefficients for CSE^{29, 30} and one for cSP²⁹. Twelve authors provided raw data for CSE^{11, 31–36, 38–41, 43}, nine for SICI^{11, 32, 34–36, 40–43}, one for LICI⁴³, six for ICF^{11, 34–37, 43}, and two for and SICF^{11, 35}. In four studies, correlation coefficients were computed from p values or t-statistics) and sample sizes for SICI^{10, 28}, ICF²⁸, SICF²⁸, cSP¹⁰, and iSP^{26, 27}. Overall, the meta-analysis included twenty Pearson's r correlation coefficients for CSE derived from fourteen studies^{11, 29–36, 38–41, 43}, thirteen for SICI from eleven studies^{10, 11, 28, 32, 34–36, 40–43}, eight for ICF from seven studies^{11, 28, 34–37, 43}, five for SICF from three studies^{11, 28, 35}, two for iSP^{26, 27} and two for cSP^{10, 29} (Table 1).

Table 1. Characteristics of included studies and correlations between physical activity and neurophysiological measures derived from transcranial magnetic stimulation

Study (Year)	N (% female)	Mean $\pm$ SD	Muscle	Physical Activity Tool (measure)	Physical Activity Outcome (Mean $\pm$ SD)	TMS measure (ISI)	r	P	Quality Score
Cirillo (2009)	28 (46)	24.4	FDI	IPAQ (MET-min/wk)	Active: 5572 $\pm$ 2075 Inactive: 491 $\pm$ 308	CSE SICI (2) cSP	0.26 0.08 0.16	0.16 0.65 0.38	12
McGregor (2011)	24 (53)	69	FDI	GLTEQ (score)	Active: 124.5 $\pm$ 83 Inactive: 52.4 $\pm$ 47 67.58 $\pm$ 33.6	iSP	0.44	0.03	14
McGregor (2013)	12 (45) 38 (57) 21 (55)	24.3 52.1 22.1	FDI	Ad-hoc questionnaire (min/week)	76.0 $\pm$ 33.4 64.7 $\pm$ 32.5	iSP iSP	n.a. 0.48 n.a.	0.002	16
Hassanlouei (2017)	24 (50) 38 (45)	22.4 $\pm$ 2.2 70.2 $\pm$ 6.1	VL	Waist Accelerometer (steps/day)	Active: 12326 $\pm$ 815 Inactive: 7133 $\pm$ 494 Active: 13565 $\pm$ 1174 Inactive: 6381 $\pm$ 402	CSE CSE	-0.18 0.02	0.39 0.9	13
Lulic (2017)	28 (60)	21 $\pm$ 1.5	FDI	IPAQ (MET-min/wk)	High: 7631 $\pm$ 6120 Low: 1305 $\pm$ 773	CSE SICI (2) SICF (1.2) SICF (2.5) ICF (10)	0.12 -0.14 0.37 -0.15 0.009	0.54 0.51 0.06 0.48 0.96	13
Houde (2018)	26 (50)	70	FDI	As-hoc questionnaire (session/wk)	$\geq$ 1: Active <1: Inactive	CSE cSP	0.225 0.124	>0.05 >0.05	13
El-Sayes (2019)	34 (50)	21 $\pm$ 2	FDI	IPAQ (MET-min/wk)	3577 $\pm$ 1893	CSE SICI (2)	-0.24 0.08	0.17 0.65	13
Rozand (2019)	27 (48) 28 (50)	72 24	FDI	Waist Accelerometer (steps/day)	Active: $\geq$ 10,000 Inactive: <10,000	CSE CSE	-0.08 0.28	0.69 0.14	12
Hu (2021)	29 (100)	19.3 $\pm$ 0.6	APB	IPAQ (MET-min/wk)	Exercise: 1655 $\pm$ 1136 Control: 1111 $\pm$ 930	CSE SICI (2.5) ICF (12)	-0.12 0.27 0.11	0.53 0.15 0.57	15
Smith (2021)	34 (44)	66.9	FDI	Wrist Accelerometer (h/wk)	6.3 $\pm$ 0.7	CSE	0.185	0.29	18
Hand (2022a)	33 (24)	32	FDI TA	IPAQ (MET-min/wk)	Active: 6488 Inactive: 1209	SICI (2) SICF (1.5) ICF (10) SICI (2) SICF (1.5) ICF (10)	-0.22 0.22 0.02 0.09 0.09 0.18	0.2 0.2 0.9 0.6 0.6 0.3	11
Hand (2022b)	28 (25)	23	FDI	IPAQ (MET-min/wk)	Active: 5850 Inactive: 1139	CSE SICI (2) SICF (1.5) ICF (10)	-0.1 0.21 -0.14 0.3	0.61 0.28 0.47 0.12	14
Curtin (2023)	20 (70) 18 (55)	25.3 64.1	FDI FDI	IPAQ (MET-min/wk)	5024 $\pm$ 4831 5683 $\pm$ 3780	ICF	-0.18 -0.39		16
Wang (2023)	40 (35)	25	FDI	PAQ (h/wk)	High: 11.6 $\pm$ 6.2 Low: 0.4 $\pm$ 0.6	CSE SICI (2) ICF (10)	0.16 0.13 0.13	0.32 0.42 0.42	12
Ross (2024)	16 (88)	27.2	APB	IPAQ (MET-min/wk)	6663 $\pm$ 5611	CSE	-0.02	0.94	16
Digonet (2025)	45 (51)	23.1 $\pm$ 3.3	FDI	IPAQ (MET-min/wk)	3274 $\pm$ 1865	CSE SICI (3)	-0.002 -0.11	0.9 0.4	
Harroum (2025)	30(50)	27(6)	FDI	IPAQ (MET-min/wk)	4647 $\pm$ 5245	CSE (110; postero-anterior) CSE (110; antero-posterior) CSE (130; postero-anterior) CSE (130; antero-posterior) SICI (2; postero-anterior) SICI (2; antero-posterior)	-0.27 0.03 -0.27 0.05 0.11 -0.09	0.13 0.8 0.13 0.93 0.54 0.6	
Houglund (2025)	15 (65) 16 (65)	27 27	FDI VL	IPAQ (MET-min/wk)	5237 (4028)	CSE CSE	0.4 -0.6	0.13 0.01	12
Farajzadeh (2026)	55 (64)	32.3	FDI	Waist Accelerometer (steps/day)	7029	CSE SICI (2) LICI (100) ICF (12)	-0.15 0.05 -0.04 -0.047	0.29 0.71 0.29 0.76	13
Gamage (2026)	54(38)	69(5.2)	APB	IPAQ (MET-min/wk)	3715 $\pm$ 2774	SICI (2)	0.14	0.2	

Notes. CSE = corticospinal excitability; cSP = cortical silent period; ICF = intracortical facilitation; IPAQ = International Physical Activity Questionnaire; iSP = ipsilateral silent period; ISI: interstimulus interval; LICI = long intracortical inhibition; LTEQ = Leisure Time Exercise Questionnaire; N = sample size; n.a. = not available; PAQ = Physical Activity Questionnaire; r = Pearson's correlation coefficient; SICF = short intracortical Facilitation; SICI = short intracortical Inhibition

4.3.3. Meta-Analysis

4.3.3.1. Corticospinal Excitability

A total of 20 correlation estimates from 16 studies (600 participants) were included in the meta-analysis examining the association between physical activity and corticospinal excitability.

The multilevel random-effects meta-analysis indicated no significant association between physical

activity and corticospinal excitability ($r = -0.03$, 95% CI $[-0.12, 0.06]$, $p = 0.51$) ([Figure 2](#)). The prediction interval ranged from -0.12 to 0.07 , indicating that future studies are expected to observe correlations ranging from small negative to small positive values. Between-study heterogeneity was negligible (total $I^2 = 0.15\%$), with virtually no variance attributable to differences between studies.

To further evaluate whether the association could be considered practically negligible, an equivalence test was conducted using equivalence bounds corresponding to a small effect size (-0.10 to 0.10). The equivalence test was significant ($Z = 1.66$, $p = 0.049$), and the 90% confidence interval (-0.100 to 0.042) fell entirely within the predefined equivalence bounds, supporting the conclusion that the association between physical activity and corticospinal excitability is negligible.

Subgroup analyses comparing physical activity measures (self-reported vs. device-based) showed no significant difference between measure types ($Q = 0.28$, $p = 0.601$). The pooled estimate was -0.05 (95% CI $[-0.16, 0.07]$, $k = 14$) for self-reported measures and $r = 0.00$ (95% CI $[-0.16, 0.17]$; $k = 6$) for device-based measures.

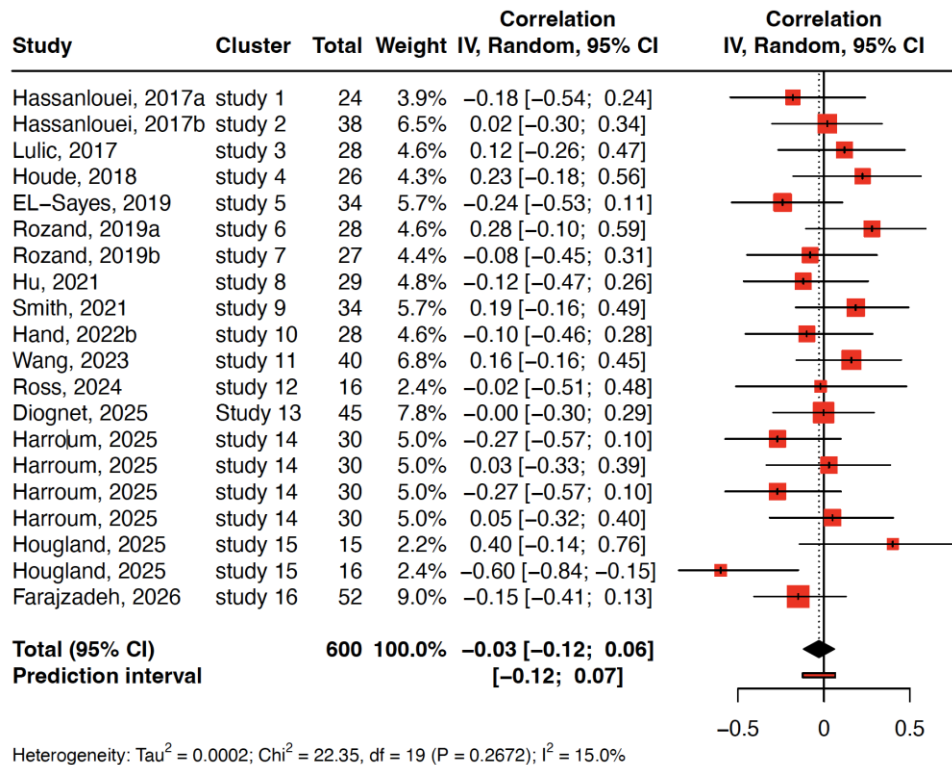


Figure 2. Forest plot of the association between physical activity and corticospinal excitability

Notes: IV = inverse variance, CI = confidence interval.

4.3.3.2. Cortical Inhibition

A total of 18 correlation estimates from 14 studies (610 participants) were included in the meta-analysis examining the association between habitual physical activity and measures of cortical inhibition. The multilevel random-effects meta-analysis indicated no significant association between physical activity and cortical inhibition ($r = 0.02$, 95% CI $[-0.10, 0.15]$, $p = 0.70$) (Figure 3). The prediction interval ranged from -0.31 to 0.35 , indicating that future studies are expected to observe correlations ranging from moderately negative to moderately positive values. Between-study heterogeneity was moderate (total I^2 of 40.99%), with variability occurring almost entirely between studies, with no meaningful heterogeneity between effect sizes within studies.

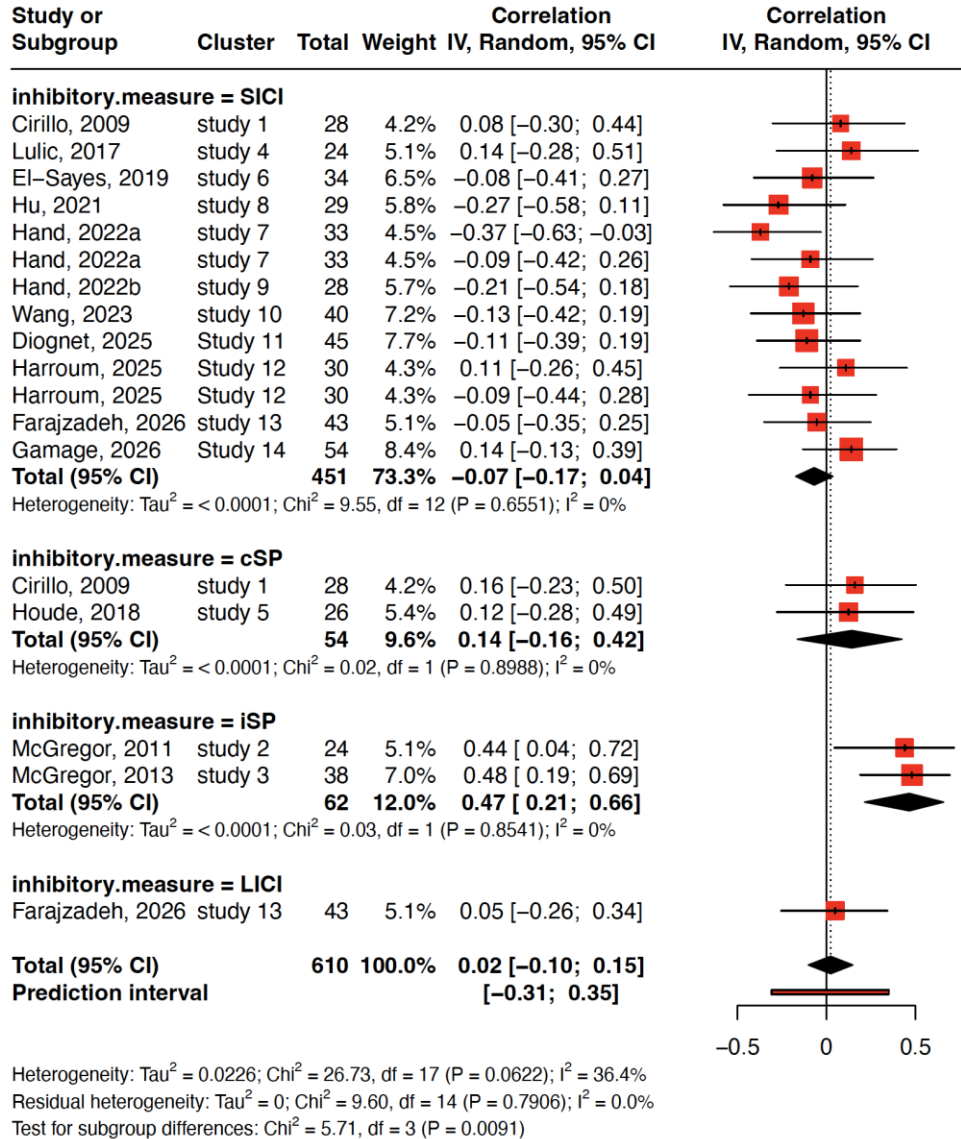


Figure 3. Forest plot of the association between habitual physical activity and TMS measures of cortical inhibition

Notes: SICI = short-interval intracortical inhibition, LICI = long-interval intracortical inhibition, cSP = cortical silent period, iSP = ipsilateral silent period, IV = inverse variance, CI = confidence interval.

The equivalence test was not significant ($Z = -1.28$, $p = 0.100$), and the 90% confidence interval (-0.074 to 0.122) extended beyond the predefined equivalence bounds. Thus, equivalence could not be concluded.

Subgroup analyses examining differences across inhibitory mechanisms (SICI, LICI, cSP, and iSP) revealed statistically significant differences between modulation types ($Q = 5.71$, $p =$

0.009) ([Figure 3](#)). The association was significant for iSP ($r = 0.47$, 95% CI [0.21, 0.66]; $k = 2$), whereas no significant associations were observed for SICI ($r = -0.07$, 95% CI [-0.17, 0.04]; $k = 13$), LICI ($r = 0.05$, 95% CI [-0.28, 0.37]; $k = 1$), or cSP ($r = 0.14$, 95% CI [-0.16, 0.42]; $k = 2$). Subgroup analyses comparing physical activity measures (self-reported vs. device-based) showed no significant difference between measure types ($Q = 0.002$, $p = 0.888$). The pooled estimate was $r = 0.03$ (95% CI [-0.11, 0.17]; $k = 16$) for self-reported measures and -0.01 (95% CI [-0.41, 0.40]; $k = 2$) for device-based measures.

4.3.3.3. Intracortical Facilitation

A total of 14 correlation estimates from 8 studies (412 participants) were included in the meta-analysis examining the association between habitual physical activity and TMS measures of cortical facilitation. The multilevel random-effects meta-analysis indicated no statistically significant association between physical activity and cortical facilitation ($r = 0.07$, 95% CI [-0.04, 0.18], $p = 0.22$). The prediction interval ranged from -0.04 to 0.18 , indicating that future studies would be expected to observe correlations ranging from slightly negative to small positive values. No meaningful heterogeneity was observed across studies ($I^2 = 0\%$), indicating that variability in the observed correlations was entirely attributable to sampling error. Variance decomposition confirmed that neither between-study nor within-study variance components contributed meaningfully to heterogeneity ([Figure 4](#)).

The equivalence test was not significant ($Z = -0.63$, $p = 0.263$), and the 90% confidence interval (-0.018 to 0.153) extended beyond the predefined equivalence bounds. Thus, equivalence could not be concluded.

Subgroup analyses comparing facilitatory measures (ICF vs. SICF) showed no significant difference between measure types ($Q = 0.002$, $p = 0.966$) ([Figure 4](#)). Point estimates were similar

for ICF ($r = 0.07$, 95% CI $[-0.07, 0.21]$; $k = 9$) and SICF ($r = 0.06$, 95% CI $[-0.13, 0.25]$; $k = 5$). Subgroup analyses comparing physical activity measures (self-reported vs. device-based) showed no significant difference between measure types ($Q = 0.59$, $p = 0.458$). The pooled estimate for self-reported measures was $r = 0.08$ (95% CI $[-0.04, 0.20]$; $k = 13$), whereas only one study and there was only a single study using a device-based measure ($r = -0.05$, 95% CI $[-0.37, 0.29]$; $k = 1$).

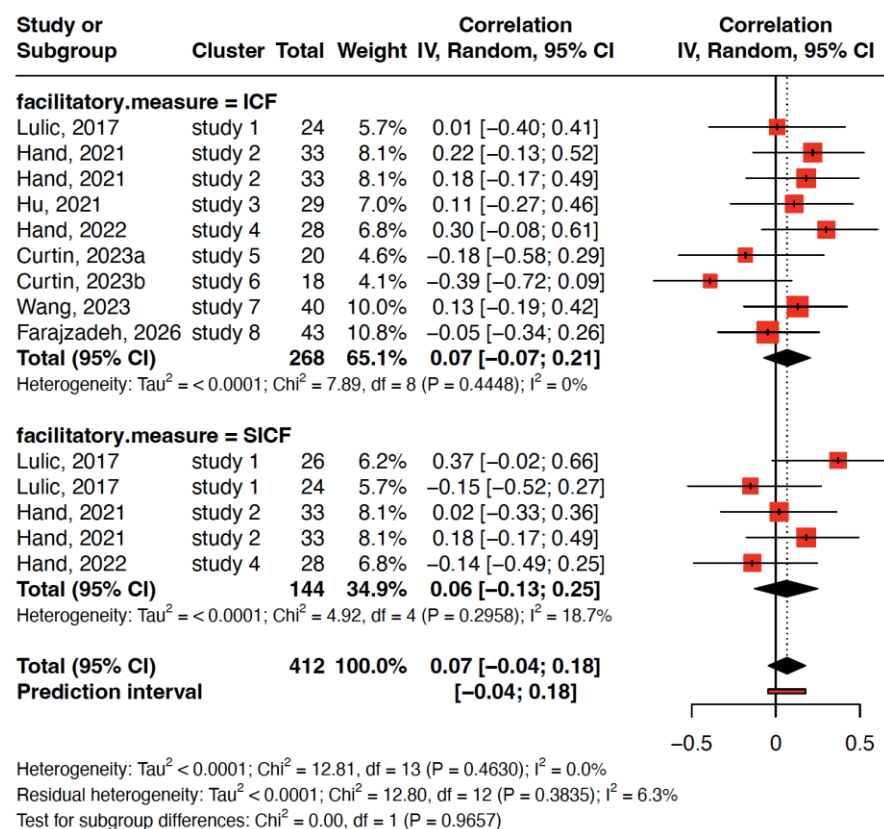


Figure 4. Forest plot of the association between habitual physical activity and transcranial magnetic stimulation measures of intracortical facilitation
Notes: ICF = intracortical facilitation, SICF = short-interval intracortical facilitation, IV = inverse variance, CI = confidence interval.

4.3.3.4. Meta-Regressions

Meta-regression analyses indicated that the association between physical activity and TMS measures was not significantly moderated by the proportion of women, mean participant age, or study quality (all $p \geq 0.105$).

4.3.3.5. Publication Bias

Potential publication bias and small-study effects were assessed using contour-enhanced funnel plots and Egger's regression tests. Visual inspection of the funnel plots for corticospinal excitability, cortical inhibition, and cortical facilitation did not reveal substantial asymmetry around the pooled effect sizes. Egger's regression tests conducted using the meta-regression approach were not statistically significant for any of the meta-analyses. The regression coefficient for the standard error was not significant for corticospinal excitability ($p = 0.86$), cortical inhibition ($p = 0.71$), or cortical facilitation ($p = 0.16$). These results indicate that smaller studies did not systematically report larger effect sizes.

4.4. Discussion

4.4.1 Main Findings

This systematic review and meta-analysis examined the association between habitual physical activity and motor cortical physiology assessed using transcranial magnetic measures. Specifically, physical activity was not statistically associated with corticospinal excitability and showed no evidence of association with cortical inhibition or intracortical facilitation. Specifically, for corticospinal excitability, the pooled correlation was close to zero, with narrow confidence intervals and negligible heterogeneity. Equivalence testing further demonstrated that this effect was statistically equivalent to zero, providing evidence that habitual physical activity is

unlikely to be meaningfully associated with corticospinal excitability. For cortical inhibition, the pooled association was small and non-significant, with moderate heterogeneity and wide prediction intervals, indicating that effects may vary across studies and populations. Subgroup analyses revealed differences across inhibitory mechanisms, with a significant positive association observed for iSP, but no significant associations for SICI, cSP, or LICI, suggesting that variability in inhibitory processes may be driven by specific neurophysiological mechanisms rather than a general effect of physical activity. For cortical facilitation, the pooled correlation was small and non-significant, with no observed heterogeneity. Equivalence testing indicated that the effect could not be considered statistically equivalent to zero. Consequently, while the available evidence does not support a meaningful relationship between habitual physical activity and cortical facilitation, small effects cannot be ruled out. Taken together, these findings suggest that habitual physical activity is not reliably associated with motor cortical physiology. Any potential relationships appear to be small, inconsistent, and dependent on specific inhibitory mechanisms rather than reflecting a global effect across motor cortical systems.

4.4.2. Acute Exercise vs Habitual Physical Activity Effects on Motor Cortical Physiology

A recent meta-analysis demonstrated that a single bout of acute aerobic exercise transiently modulates motor cortical physiology⁶. Specifically, acute aerobic exercise produced a small increase in SICI ($g = 0.27$), with stronger effects observed at moderate and high exercise intensities, and these changes persisted for up to 30 minutes following exercise. In contrast, increases in CSE were observed only following high-intensity exercise and were generally small in magnitude, while effects on ICF and LICI were not statistically significant. In comparison, the present meta-analysis of habitual physical activity revealed no reliable associations with CSE, cortical inhibition, or cortical facilitation. Notably, CSE was statistically equivalent to zero,

indicating that the transient increases observed following acute exercise do not translate into persistent differences in corticospinal output. For inhibitory processes, although no overall association with habitual physical activity was observed, variability across studies was substantial and appeared to be driven by specific mechanisms, with iSP showing a significant positive association, in contrast to the absence of effects for SICI, cSP, and LICI. Facilitation (ICF/SICF) similarly showed no significant or equivalent effects, suggesting that any relationship with habitual physical activity is likely small or inconsistent.

Together, these findings suggest a dissociation between the transient neurophysiological effects of acute exercise and the absence of consistent long-term adaptations associated with habitual physical activity. Acute exercise appears to induce short-lived modulation of motor cortical circuits, particularly within inhibitory networks, whereas habitual physical activity is not associated with stable, global changes in motor cortical physiology. Instead, any long-term adaptations may be subtle, context-dependent, and restricted to specific inhibitory mechanisms such as interhemispheric interactions. These results further suggest that GABAergic inhibitory circuits may be acutely sensitive to exercise, but do not necessarily exhibit sustained plastic changes in relation to habitual physical activity levels.

4.4.3. Limitations

Several limitations should be considered when interpreting the findings of this systematic review and meta-analysis. First, the analyses were based on correlational data and therefore do not permit conclusions regarding causal relationships. Second, the available literature was limited for several TMS-derived measures of motor cortical physiology. While sufficient studies were available to synthesize associations for CSE, cortical inhibition, and intracortical facilitation, the number of studies examining each specific inhibitory and facilitatory process was relatively low.

Third, most studies assessing physical activity relied on self-reported questionnaires, which may be subject to recall bias and measurement error compared with device-based approaches such as accelerometry. Fourth, many eligible studies did not report the correlation coefficients or sufficient statistical information required for meta-analysis. Of the 53 studies that met our inclusion criteria, usable data were available for only 17 (36%). This limited data availability raises the possibility of availability bias and may have influenced the pooled estimates. Finally, variability in TMS methodologies across studies (e.g., including differences in stimulation parameters, interstimulus intervals, and participant characteristics) may have contributed to heterogeneity in the reported neurophysiological measures. Future research using larger samples, standardized neurophysiological protocols, and objective assessments of physical activity will be important to better clarify the relationship between habitual physical activity and motor cortical physiology. Additionally, the correlations synthesized in this meta-analysis were derived from heterogeneous combinations of physical activity metrics and neurophysiological outcomes, which may not be directly comparable. However, the low heterogeneity observed for corticospinal excitability and intracortical facilitation suggests that this variability did not meaningfully influence effect estimates. In contrast, moderate heterogeneity observed for cortical inhibition appeared to be driven primarily by differences across inhibitory mechanisms rather than by physical activity measurement.

4.5. Conclusion

Overall, these findings suggest that habitual physical activity is unlikely to be associated with global or robust differences in motor cortical neurophysiology. Future studies using larger samples, standardized TMS protocols, and objective assessments of physical activity are needed to determine whether physical activity may instead relate to more specific or higher-order neural processes beyond M1.

4.6. Data Availability

The data and analysis scripts used in this study are available in a public repository (<https://github.com/Boisgontier-Lab/TMS-MetaAnalysis>).

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Chapter 5

Behavioral Apathy Shows Negligible Associations with M1 Corticospinal Excitability and Intracortical Circuits

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5.1. Introduction

Apathy is a multidimensional syndrome of diminished motivation characterized by reduced goal-directed behavior, diminished goal-related cognition, and blunted emotional responsiveness to success or failure^{1, 2}. Although apathy is often examined in neurological and psychiatric conditions, it is not confined to clinical populations. Rather, it varies in degree and is observed across the lifespan, including in otherwise healthy adults^{3–12}. This broader distribution suggests that apathy reflects a continuum of motivational functioning rather than a phenomenon exclusive to disease.

Current neurocognitive accounts link apathy to dysfunction within fronto-striatal circuits involved in valuation, action selection, and motor output, including the prefrontal cortex, anterior cingulate cortex, ventral striatum, and SMA^{9, 10, 13}. Neuroimaging studies have consistently associated apathy with structural and functional alterations in these regions and pathways^{14–17}. However, the extent to which apathy is related to the neurophysiological properties of the M1 remains unclear. This question is important because M1 is embedded within broader motor and cognitive-control networks and is strongly interconnected with supplementary motor and cingulo-prefrontal regions that have been implicated in apathy^{18–21}.

Among the dimensions of apathy, behavioral apathy is the most directly related to action. It refers to reduced self-initiated, goal-directed behavior and a diminished capacity to translate intentions into spontaneous activity in the absence of external prompting^{13, 22, 23}. Because the initiation of goal-directed behavior ultimately requires the recruitment of motor pathways, behavioral apathy may be especially relevant to neural systems that couple motivational processes with motor output. In this respect, it provides a useful dimension for examining whether variation in motor cortical neurophysiology is associated with reduced self-initiated behavior.

Despite increasing interest in the neurobiology of apathy, it remains unclear whether individual differences in behavioral apathy are associated with motor cortical function, as measured by transcranial magnetic stimulation (TMS). A recent study investigated the relationship between global apathy and fronto-motor circuits but did not specifically focus on behavioral apathy and intracortical motor pathways ²⁴. As a result, it remains unclear whether behavioral apathy is associated with corticospinal excitability or with intracortical inhibitory and facilitatory mechanisms within M1. Addressing this gap may clarify whether reduced self-initiated behavior is associated not only to higher-order motivational and decision-related systems, but also to local cortical circuit properties of M1.

Accordingly, the aim of the present study was to determine whether TMS measures used to evaluate M1 function are associated with behavioral apathy. Specifically, we examined corticospinal excitability (CSE), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and intracortical facilitation (ICF). We tested whether these measures were associated with behavioral apathy.

5.2. Methods

5.2.1. Participants

Healthy adults aged 18 to 60 years with no history of neurological disease were recruited through posters displayed at the University of Ottawa Faculty of Health Sciences. Handedness was assessed using the Edinburgh Handedness Inventory ²⁵. Participants were screened for contraindications to TMS ²⁶. The study was approved by the University of Ottawa Research Ethics Board (H-11-24-10863) and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent. Data were collected between June and September 2025. Participants were not compensated for their participation. In addition, an existing unpublished

dataset from a previous study ²⁴, containing the same variables as those collected in the present study, was obtained directly from the authors by email and pooled with the newly collected data.

5.2.2. Sample Size Justification

Given the absence of prior studies examining the association between behavioral apathy and TMS measures of M1 excitability, including corticospinal and intracortical measures, no effect size estimate was available to inform an a priori power analysis. Rather than relying on generic benchmarks, the sample size was justified based on a sensitivity analysis ²⁷ conducted in G*Power 3.1 for a linear multiple regression model including each TMS parameter as the predictor of interest and four covariates (age, gender, depressive symptoms, and data source). Assuming a two-sided $\alpha = .05$ and power $(1 - \beta) = .90$, a sample size of $N = 100$ provides sensitivity to detect an effect size of $f^2 = 0.107$, corresponding approximately to a partial correlation of $r = .31$. Smaller effects remain estimable, but with less precision.

5.2.3. Procedure

Following enrollment, participants completed self-report questionnaires assessing apathy and depressive symptoms. They then took part in a single TMS session with the order of neurophysiological testing randomized across participants. Sessions were scheduled at approximately the same time of day (± 3 h) to account for diurnal fluctuations in corticospinal excitability ²⁸. The TMS session included the following steps: motor cortex hotspot identification, resting motor threshold (RMT) determination, assessment of corticospinal excitability using single-pulse TMS, and assessment of intracortical inhibition and facilitation using paired-pulse TMS.

5.2.4. Behavioral Apathy

Self-reported behavioral apathy was assessed using the Action Initiation subscale of the extended Lille Apathy Rating Scale (LARS-e), an 11-item questionnaire^{15, 29}. Participants rated the extent to which each statement reflected their own behavior on a 1-to-5 Likert scale, with 1 corresponding to extremely apathetic and 5 to extremely motivated. Scores were reverse coded so that higher values reflected greater behavioral apathy. We used the mean score per item in the analyses.

5.2.5. Depressive Symptoms

Depressive symptoms were assessed using the Depression subscale of the Depression Anxiety Stress Scale (DASS; DASS-42 in the current study and DASS-21 in the retrieved dataset)³⁰. Participants indicated the extent to which each statement applied to them over the past week using a 0-to-3 Likert scale, with 0 corresponding to “did not apply to me at all” and 3 to “applied to me very much of the time”. We used the mean score per item in the analyses, with higher scores indicating greater depressive symptoms.

5.2.6. Electromyography Recording

Electromyography was recorded from the right first dorsal interosseous (FDI) muscle using 9-mm Ag-AgCl surface electrodes placed in a belly-tendon montage. A wet ground electrode was placed around the forearm. Electromyographic signals were amplified ($\times 1000$), band-pass filtered (20–450 Hz), and digitized at 5 kHz using a Micro 1401 system (Cambridge Electronic Design, Cambridge, UK). Data were acquired using Signal software version 8.01 (Cambridge Electronic Design, Cambridge, UK). Electromyographic activity was recorded in 1000-ms sweeps, from 100 ms before to 900 ms after TMS delivery. EMG recordings were visually inspected prior to analysis,

and trials contaminated by voluntary muscle activity during the 100 ms preceding the TMS pulse were excluded, as preactivation can influence MEP amplitude.

5.2.7. Transcranial Magnetic Stimulation

Single- and paired-pulse monophasic TMS was delivered using a figure-of-eight coil connected to a Magstim BiStim stimulator (Magstim, Whitland, UK). The coil was positioned over the optimal scalp location for eliciting motor-evoked potentials (MEPs) in the relaxed right FDI muscle. It was oriented at 45° to the parasagittal plane to induce a posterior-to-anterior current in the cortex. The motor hotspot was defined as the location over the left M1 that consistently elicited the largest MEPs in the relaxed right FDI. This location was marked using theBrainsight neuro-navigation system (Rogue Research, Canada) with a standard magnetic resonance imaging template. RMT was determined for the right FDI and defined as the lowest stimulation intensity required to evoke MEPs of at least 50 μ V in 5 out of 10 consecutive trials in the relaxed muscle³¹.

5.2.7.1. Corticospinal Excitability (CSE)

CSE was assessed by recording MEPs from the resting right FDI following single-pulse TMS delivered at 120% of each participant's RMT. Approximately 20 to 30 stimuli were delivered per participant³², with intertrial intervals jittered between 5 and 7 s, consistent with recommendations for reliable estimation of corticospinal excitability³³. EMG data were visually inspected to confirm the absence of voluntary muscle activity before stimulation. Peak-to-peak MEP amplitudes (mV) were extracted on a trial-by-trial basis using Signal software and averaged across valid trials to derive the measure of CSE. Larger amplitudes indicated greater corticospinal excitability^{34, 35}.

5.2.7.2. Intracortical Inhibition (SICI) and Facilitation (ICF)

SICI and ICF were assessed using paired-pulse TMS delivered over the M1 hotspot. In both protocols, a subthreshold conditioning stimulus was followed by a suprathreshold test stimulus. Interstimulus intervals were 2 ms for SICI and 12 ms for ICF. The conditioning stimulus was delivered at 80% of RMT, and the test stimulus intensity was adjusted to elicit an unconditioned MEP of approximately 1 mV in the resting FDI^{35–37}. For each interstimulus interval, approximately 20 to 30 paired-pulse trials were delivered, along with 10 to 12 single-pulse test trials. SICI and ICF were quantified as the ratio of conditioned to unconditioned MEP amplitudes (paired-pulse MEP / single-pulse MEP). For SICI, smaller ratios indicate greater inhibition, whereas for ICF, larger ratios indicate greater facilitation.

5.2.7.3. Long-Interval Intracortical Inhibition (LICI)

LICI was assessed using two suprathreshold pulses separated by an interstimulus interval of 100 ms. Both pulses were delivered at the test-stimulus intensity required to evoke an MEP of approximately 1 mV^{35–37}. LICI was quantified as the ratio of the conditioned MEP elicited by the second pulse to the unconditioned MEP elicited by the first pulse, with smaller values indicating greater inhibition.

5.2.8. Statistical Analysis

We examined the association between behavioral apathy and each TMS measure using separate multiple linear regression models. Behavioral apathy was the dependent variable and was analyzed as a mean item score ranging from 1 to 5. Four models were estimated, each including one TMS predictor: CSE, SICI, LICI, and ICF. Each model adjusted for age, gender, depressive symptoms, and data source. All continuous predictors were standardized prior to analysis using z-

scores. Gender and data source were entered as factors. Missing data were handled using listwise deletion within each model (na.omit), resulting in slightly different sample sizes across models. In addition to conventional null-hypothesis significance testing, we conducted equivalence tests using the two one-sided tests procedure for the coefficient of the TMS measure in each regression model. In the absence of an established minimally important difference for this measure, equivalence bounds were set at -0.2 and 0.2 , which were interpreted as representing a small and negligible difference on the 1–5 mean behavioral apathy scale. Because the TMS predictors were standardized, the regression coefficients represent the expected change in mean apathy score associated with a 1-standard-deviation increase in the predictor. Because behavioral apathy was analyzed on its raw mean scale, the equivalence bounds indicate that changes in mean apathy score smaller than 0.20 points were considered negligible. Equivalence was concluded when both one-sided tests were significant at $\alpha = .05$, which is equivalent to the 90% confidence interval lying entirely within the equivalence bounds.

5.2.8.1. Sensitivity Analysis

To assess the robustness of our findings, we conducted a sensitivity analysis using more stringent exclusion criteria. Trials with MEP amplitudes outside expected physiological ranges were excluded. Specifically, we excluded trials exceeding 0.7 mV for SICI and LICI, and trials with values below 1.3 for ICF from our dataset.

5.3. Results

5.3.1. Descriptive Results

The sample comprised 100 participants, of whom 64% were women and 36% were men. Participants were drawn from two data sources, with 45% from an unpublished dataset retrieved from a previous study ²⁴ and 55% from the current study. The mean age was 28.9 ± 6.33 years

(mean $\pm$ SD). The behavioral apathy score was 1.49 ± 0.59 , and the DASS depression score was 0.62 ± 0.62 (Figure 1). For the TMS measures, the mean values were 0.61 ± 0.41 mV for CSE, 0.34 ± 0.23 for SICI, 0.15 ± 0.21 for LICI, and 1.35 ± 0.51 for ICF (Figure 1). Because missing data were handled using listwise deletion within each model, the analytic sample size varied slightly across regression analyses, ranging from $n = 90$ for LICI to $n = 97$ for CSE, with $n = 92$ for SICI and $n = 91$ for ICF.

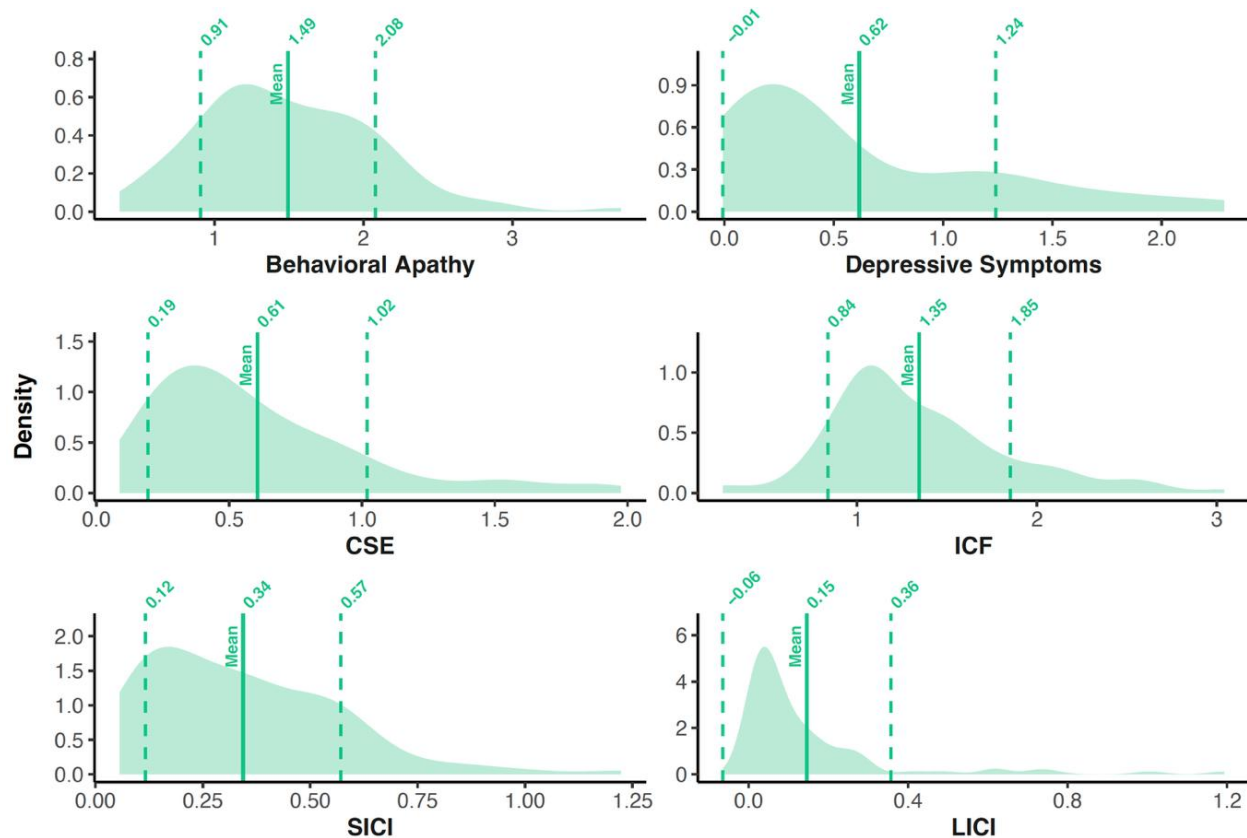


Figure 1. Distributions of behavioral apathy, depressive symptoms, and TMS measures

Note. Faceted density plots illustrating the distributions of behavioral apathy, depressive symptoms, and the TMS measures. In each panel, the solid vertical line marks the mean and the dashed vertical lines mark one standard deviation below and above the mean. Numeric labels indicate the corresponding values. CSE = corticospinal excitability, ICF = intracortical facilitation, SICI = short-interval intracortical inhibition, LICI = long-interval intracortical inhibition

Table 1. Adjusted associations of corticospinal excitability (CSE), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and intracortical facilitation (ICF) with behavioral apathy

	CSE (n = 97)			SICI (n = 92)			LICI (n = 90)			ICF (n = 91)		
Variable	b	95CI	P	b	95CI	P	b	95CI	p	B	95CI	p
(Intercept)	1.58	1.33 ;1.84	<.001 ***	1.67	1.41 ;1.93	<.001 ***	1.68	1.41 ;1.94	<.001 ***	1.69	1.42 ;1.95	<.001 ***
Age	0.065	-0.08 ;0.21	.359	0.10	-0.05 ;0.24	.185	0.11	-0.04 ;0.25	.141	0.12	-0.03 ;0.26	.114
Gender	-0.05	-0.29 ;0.20	.704	-0.14	-0.40 ;0.11	.261	-0.14	-0.41 ;0.11	.267	-0.16	-0.42 ;0.10	.226
Data source	-0.12	-0.41 ;0.16	.404	-0.18	-0.47 ;0.11	.226	-0.19	-0.48 ;0.10	.197	-0.19	-0.47 ;0.10	.190
DASS	0.16	-0.04 ;0.27	.011 *	0.16	0.03 ;0.28	.012 *	0.16	0.04 ;0.28	.012 *	0.16	0.03 ;0.28	.013 *
CSE	0.01	-0.12 ;0.13	.902									
SICI				-0.03	-0.16 ;0.09	.633						
LICI							-0.02	-0.15 ;0.10	.698			
ICF										-0.05	-0.18 ;0.08	.465
R ²		.085			.111			.114			.114	
Adjusted R ²		.035			.059			.062			.062	
F, Model p		1.69, p = .145			2.14, p = .068			2.17, p = .065			2.19, p = .063	

Note. *p<.05, ***p<.001, b = unstandardized regression coefficient, 95CI = 95% confidence interval, DASS = Depression subscale of the Depression Anxiety Stress Scale, R² = coefficient of determination, adjusted R² = coefficient of determination adjusted for the number of predictors in the model, F = overall model test statistic.

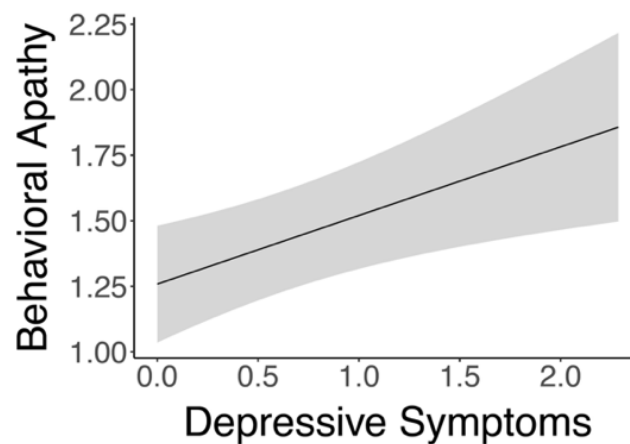


Figure 2. Adjusted association between behavioral apathy and depressive symptoms

Note. Predicted behavioral apathy across the observed range of depressive symptoms. The solid line represents model-based predicted values, and the shaded band represents the 95% confidence interval. Behavioral apathy and depressive symptoms are shown as the mean per-item score.

5.3.2. Statistical Results

The adjusted regression analyses showed no evidence that behavioral apathy was significantly associated with any of the four TMS measures: CSE ($b = 0.01$, 95% CI $[-0.12, 0.13]$, $p = .902$), SICI ($b = -0.03$, 95% CI $[-0.16, 0.09]$, $p = .633$), LICI ($b = -0.02$, 95% CI $[-0.15, 0.10]$, $p = .698$), and ICF ($b = -0.05$, 95% CI $[-0.18, 0.08]$, $p = .465$) (Table 1). In contrast,

depressive symptoms were positively associated with behavioral apathy scores in all four models (all $bs = 0.16$, 95% CIs [0.03, 0.28], all $ps \leq .013$) ([Figure 2](#)).

Equivalence testing showed that the effects of all TMS measures fell within the negligible-effect interval of -0.2 to 0.2 apathy-score units per 1-standard-deviation increase in the predictor ([Figure 3](#)). Specifically, the 90% confidence intervals were $[-0.10, 0.11]$ for CSE, $[-0.13, 0.07]$ for SICI, $[-0.13, 0.08]$ for LICI, and $[-0.16, 0.06]$ for ICF. Corresponding p values were .001, .004, .003, and .010, respectively, indicating equivalence for all four TMS measures. Overall, these findings indicate that the adjusted associations of M1 corticospinal excitability, intracortical inhibition, and facilitation with behavioral apathy were sufficiently small to be considered negligible.

5.3.2.1. Sensitivity Analysis

The sensitivity analysis using more stringent exclusion criteria resulted in the removal of 3.3% of trials. Results were consistent with the primary analysis ([Appendix D, Suppl. Material 1](#)), indicating that the findings are robust to these alternative exclusion thresholds.

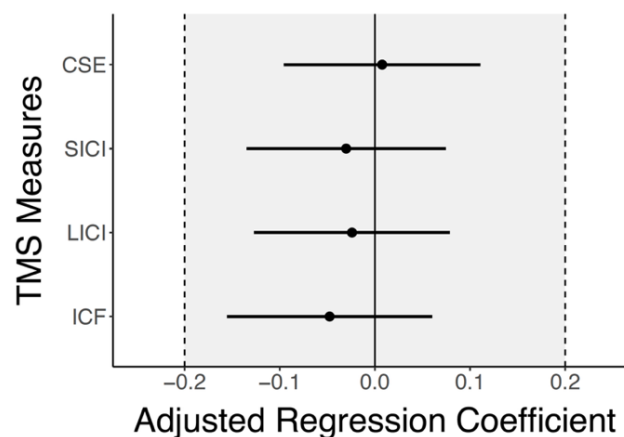


Figure 3. Equivalence of associations between behavioral apathy and TMS measures

Note. Adjusted regression coefficients (points) and 90% confidence intervals (whiskers) for the associations between behavioral apathy and each TMS measure. The shaded region represents the equivalence interval (-0.2 to 0.2), and dashed vertical lines indicate its boundaries. Effects were considered statistically equivalent to zero when their 90% confidence intervals fell entirely within these bounds.

5.4. Discussion

5.4.1. Principal Findings

The results provide converging evidence that behavioral apathy is not meaningfully associated with motor cortical function. All regression coefficients relating TMS measures to behavioral apathy were small and non-significant. Critically, equivalence testing indicated that any true associations, if present, are likely too small to be relevant. In contrast, depressive symptoms were consistently associated with higher behavioral apathy scores. This finding supports the construct validity of the behavioral apathy measure and aligns with prior evidence that apathy and depressive symptoms are positively related, but distinct, dimensions of reduced motivation³⁸.

5.4.2. Comparison with the Literature

The current findings are consistent with neurocognitive models that primarily locate apathy within fronto-striatal and cingulo-prefrontal circuits involved in valuation, decision-making, and action initiation^{9, 13}. While these models acknowledge the role of motor systems in translating motivation into action, they do not typically posit that apathy originates from dysfunction at the level of M1. Previous neuroimaging studies have linked apathy to alterations in regions such as the anterior cingulate cortex, ventral striatum, and SMA, rather than to M1 in isolation^{14, 17, 24}. The present results align with this literature by suggesting that the neurobiological substrates of behavioral apathy may lie upstream of M1, in circuits responsible for generating and selecting goal-directed actions, rather than in the execution-related properties of corticospinal output. Our findings also extend prior work using TMS in the context of apathy. For example, Derosiere and collaborators examined fronto-motor circuits in relation to global apathy, emphasizing connectivity between frontal regions, basal ganglia, and motor regions²⁴. By specifically targeting behavioral apathy and M1 physiology, the present study provides a more fine-grained test of

whether reduced self-initiated behavior is linked to local M1 cortical excitability. The absence of associations with M1 output suggests that behavioral apathy does not primarily reflect a deficit in corticospinal excitability at rest.

Importantly, this does not exclude a role for motor systems in apathy. Rather, it suggests that motor-related contributions are more likely to involve higher-order motor planning or motivational gating processes, potentially mediated by premotor or medial frontal regions and their interactions with M1, rather than baseline excitability within M1 itself.

5.4.3. Limitations

Several limitations should be considered when interpreting these findings. First, the sample consisted of healthy young adults with relatively low levels of behavioral apathy and depressive symptoms. This restricted range limits generalizability to clinical populations, in whom apathy may be more pronounced and may be associated with detectable neurophysiological alterations. Second, although the sample size was justified by a sensitivity analysis and was sufficient to detect small-to-moderate effects, very small associations may have gone undetected. However, the use of equivalence testing mitigates this concern by demonstrating that any such effects are likely negligible within a meaningful range. Third, TMS measures were obtained at rest and reflect baseline properties of corticospinal and intracortical circuits. Fourth, although we adjusted for depressive symptoms, age, gender, and data source, other potentially relevant factors, such as fatigue, sleep quality, or personality traits, were not included and may contribute to variability in both apathy and motor cortical measures. Finally, the pooling of newly collected data with an existing dataset increased statistical power but may have introduced heterogeneity, despite adjustment for data source in the analyses.

5.5. Conclusion

This study provides evidence that behavioral apathy is not meaningfully associated with M1 excitability, including corticospinal and intracortical circuits in healthy adults. By combining regression analyses with equivalence testing, the results indicate that any such associations are negligibly small. These findings suggest that reduced self-initiated goal-directed behavior is unlikely to be explained by physiological properties of M1. Instead, behavioral apathy may primarily reflect alterations in higher-order motivational systems^{15, 24}.

5.6. Data Availability

The data and analysis scripts used in this study are publicly available in a public repository (<https://github.com/Boisgontier-Lab/TMS-apathy>).

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Chapter 6

General Discussion

6.1. Overview

Apathy can affect several domains of functioning, ranging from cognition and executive processes to emotional engagement (Onyike et al., 2007; Geda et al., 2008; Brodaty et al., 2010; Kawagoe et al., 2017) and physical behavior (Vanner et al., 2008; Farholm et al., 2017; Ringen et al., 2018; Farajzadeh et al., 2025). In both clinical and non-clinical populations, it has been associated with poorer cognitive performance, reduced social participation, and greater functional decline (Montoya-Murillo et al., 2019; Ayers et al., 2017; Barone et al., 2009; Vilalta-Franch et al., 2013), highlighting that apathy is not only a clinical concern but also a broader public health issue that may interfere with engagement in health-promoting behaviors. One important pathway through which apathy may exert its impact on physical health is through reduced engagement in physical activity. Given the well-established role of physical activity in maintaining physical, cognitive, and mental health, understanding factors that may hinder physical activity engagement is of substantial clinical and public health importance. Therefore, this thesis focused on the relationship between apathy and physical activity. Specifically, it aimed to better understand how motivational processes influence engagement in active behavior, with a particular focus on behavioral and neurophysiological factors in healthy adults.

The driving force for this thesis was based on the idea that physical inactivity may not be explained only by lack of knowledge (Bauman et al., 2012), lack of intention (Rhodes et al., 2013), or environmental barriers (Wendel-Vos et al., 2007). Rather, motivational factors such as apathy may play a role in whether individuals initiate and sustain physical activity. This is particularly relevant because physical activity requires effort, planning, initiation, and persistence, all of which may be compromised in individuals with levels of behavioral apathy. Therefore, understanding the

relationship between apathy and physical activity may help identify why some individuals struggle to engage in physical activity despite its well-established benefits.

The present thesis focused specifically on behavioral apathy, as it is directly related to action. While cognitive and emotional apathy may influence planning, interest, or emotional engagement, behavioral apathy reflects reduced self-initiation and persistence (Levy & Dubois, 2006). This is particularly relevant in the context of physical activity, which requires overcoming effort costs, initiating action, and sustaining behavior over time.

The relationship between behavioral apathy and physical activity may be shaped by both behavioral and neurophysiological factors. From a behavioral perspective, we hypothesized that affective attitudes toward physical activity represent a key mechanism underlying this association. Individuals who perceive physical activity as unpleasant or effortful may be less likely to initiate or maintain such behavior. Given that behavioral apathy is characterized by reduced self-initiation and greater sensitivity to effort costs, affective attitudes may be particularly relevant in understanding this relationship.

From a neural perspective, prior work suggests that higher behavioral apathy is associated with altered effort sensitivity and changes in action-related networks, particularly involving the anterior cingulate cortex and SMA (Bonnelle et al., 2016; Derosiere et al., 2025). Given the role of these fronto-striatal and motor-related circuits in valuation, action initiation, and motor output, this provided the basis for examining whether behavioral apathy is reflected in neurophysiological markers of motor system function. We hypothesized that behavioral apathy would be associated with TMS-derived indices of motor cortical function. In addition, we assessed whether physical activity is associated with these measures and hypothesized that motor cortical neurophysiology would contribute to, and potentially mediate, the relationship between apathy and physical activity.

This thesis examined the relationship between apathy, physical activity, attitudes toward physical activity, and motor cortex neurophysiology through four steps. First, we systematically reviewed the association between physical activity and apathy. Second, we investigated the relationship between behavioral apathy, physical activity, and attitudes toward physical activity. Third, we systematically reviewed the association between physical activity and motor cortex neurophysiology. Fourth, we investigated whether behavioral apathy is associated with these same neurophysiological parameters.

Together, these objectives were designed to build a stepwise understanding of the apathy–physical activity relationship. The first two objectives addressed the behavioral and motivational side of this relationship, while the later objectives examined whether M1 neurophysiology may represent a potential biological pathway linking apathy and physical activity. This approach is important because it moves beyond simply asking whether apathetic individuals are less physically active and instead asks why this relationship may occur and whether it is reflected in measurable neurophysiological differences.

6.2. Apathy as a Barrier to Physical Activity

The systematic review and meta-analysis provided the foundation for this thesis by demonstrating that apathy is negatively associated with physical activity. This finding supports the central premise that apathy may represent an important motivational barrier to engagement in active behavior. Although the pooled association was small in the main analysis, it was consistent with the expected pattern that reduced motivation, initiative, and persistence can interfere with the ability to initiate and maintain physical activity. This finding suggests that physical inactivity should not be understood only as a consequence of poor knowledge, weak intention, or limited access to opportunities. Rather, for some individuals, reduced physical activity may reflect

difficulty with self-initiation and effort-based engagement. Physical activity requires individuals to evaluate the expected benefits of action, tolerate immediate effort costs, and persist over time. Therefore, individuals with higher levels of apathy may be less likely to engage in physical activity because the perceived cost of action outweighs its expected reward.

The subgroup analyses further suggest that the relationship between apathy and physical activity may vary across populations. The association appeared particularly pronounced in individuals with Parkinson's disease and in older adults, suggesting that age-related and disease-related changes may amplify the impact of apathy on physical activity. In Parkinson's disease, dopaminergic dysfunction may increase the perceived cost of effort and reduce willingness to engage in activity (Martínez-Horta et al., 2014; Muhammed et al., 2016). This interpretation aligns with decision-making models of goal-directed behavior, in which individuals weigh expected rewards against anticipated effort costs before initiating action. Similarly, in older adults, the higher energetic cost of movement and age-related declines in physical efficiency may make physical activity more effortful, thereby strengthening the negative influence of apathy on engagement in physical activity.

The systematic review and meta-analysis also provided important methodological insight. The negative association between apathy and physical activity was observed across multiple apathy measures and across both self-reported and device-based physical activity outcomes. This supports the robustness of the relationship and suggests that the association is not simply an artifact of a specific measurement approach.

Taken together, these findings supported the notion that apathy is meaningfully associated with lower physical activity and may represent a clinically relevant barrier to engagement in active behavior. However, the correlational nature of the available evidence means that the direction of

this relationship remains uncertain. Apathy may reduce physical activity by impairing motivation and self-initiation, while lower levels of physical activity may also contribute to greater apathy through reduced exposure to rewarding experiences, poorer mental health, or functional decline. It is also possible that this relationship is bidirectional and shaped by underlying behavioral and neurophysiological mechanisms, as discussed in the following sections.

6.3. Behavioral Mechanisms Linking Apathy and Physical Activity

The systematic review and meta-analysis established that apathy is negatively associated with physical activity, but it did not clarify the mechanisms underlying this relationship. In addition, much of the existing literature has relied on global apathy measures, leaving a gap in understanding the specific role of behavioral apathy, which is more directly related to action initiation (Levy & Dubois, 2006). This limitation is important because identifying an association is only the first step; understanding why individuals with higher apathy are less physically active is necessary for developing more targeted interventions. Therefore, the next study moved beyond examining whether apathy is related to physical activity and focused on behavioral mechanisms that may explain this relationship.

Specifically, this study focused on intentions, explicit affective attitudes, and approach–avoidance tendencies toward physical activity, as these reflect key reflective and automatic motivational processes through which behavioral apathy may influence engagement. These processes reflect how individuals form intentions, evaluate physical activity, and respond to effort-related movement cues. Intentions represent the most proximal determinant of behavior, although they are not always sufficient to ensure action (Ajzen, 2011; Biddle et al., 2007; Rhodes & de Bruijn, 2013). In parallel, dual-process models indicate that behavior is shaped by both reflective processes (e.g., intentions, explicit attitudes) and automatic processes (e.g., approach–avoidance

tendencies) (Brand & Ekkekakis, 2017; Cheval & Boisgontier, 2021). Together, these processes provided a framework for understanding how apathy may translate into reduced engagement in physical activity.

The findings showed that higher behavioral apathy was associated with lower physical activity, and that this relationship was partially mediated by weaker intentions to be physically active. This suggests that apathy may reduce physical activity, at least in part, by weakening the motivational commitment required to initiate and sustain goal-directed behavior, consistent with its conceptualization as a motivational impairment (Levy & Dubois, 2006; Marin, 1990; Marin, 1991). In line with this, apathy may reduce the effort individuals are willing to invest in physical activity, potentially reflecting increased sensitivity to effort or reduced sensitivity to reward (Bonnelle et al., 2015; Pessiglione et al., 2017). Importantly, explicit affective attitudes mediated the relationship between behavioral apathy and intentions to be physically active, providing a more specific account of how apathy may interfere with engagement. Individuals with higher apathy may perceive physical activity as less pleasant or more effortful, which may reduce their intention to be active. This interpretation is consistent with studies that affective evaluations, based on anticipated emotional experiences, play a central role in shaping intentions and subsequent behavior (Stevens et al., 2020; Williams & Evans, 2014; Ekkekakis, 2017). Accordingly, affective attitudes appear to represent a key behavioral pathway through which apathy translates into reduced physical activity.

The approach–avoidance findings further support this interpretation. Individuals with lower apathy showed stronger tendencies to approach physical activity stimuli and avoid sedentary stimuli, whereas these tendencies weakened as apathy increased. Although these tendencies did not mediate the relationship between apathy and intentions or physical activity, they indicate that

apathy may still influence automatic motivational responses toward activity-related cues. This pattern is consistent with the role of approach–avoidance tendencies in guiding behavior (Elliot et al., 2013; Sander et al., 2018) and may reflect altered effort–reward processing in individuals with higher apathy (Bonnelle et al., 2015; Martínez-Horta et al., 2014; Muhammed et al., 2016). Thus, while reflective processes appear to play a more central role, behavioral apathy may also shape physical activity through altered approach–avoidance dynamics.

Together, these findings extend the results of the systematic review and meta-analysis by showing that the association between apathy and physical activity is not only observed but also partly explained by underlying motivational and affective processes. In particular, the results suggest a pathway in which higher behavioral apathy is associated with less positive explicit attitudes toward physical activity, which in turn weakens intentions to be physically active and ultimately contributes to lower physical activity engagement. This supports the broader argument of the thesis that physical inactivity in individuals with apathy may reflect difficulties in translating motivational value into action.

These findings have practical implications for supporting physical activity in individuals with higher apathy. Rather than focusing only on education or exercise prescription, it may be more effective to address the motivational processes that influence behavior. For example, helping individuals experience physical activity as more enjoyable, less effortful, and easier to initiate may support engagement. Providing structure and external support may also be beneficial, as individuals with higher apathy may have difficulty initiating activity on their own. Overall, these findings suggest that reduced physical activity in apathy may be related to how effort and reward are perceived.

Addressing this objective helped clarify the behavioral mechanisms linking apathy and physical activity. However, these factors alone are unlikely to fully account for the relationship. Given that apathy has been linked to alterations in fronto-striatal and motor-related networks involved in effort-based decision-making and action initiation, the next step was to examine whether neurophysiological factors also contribute to this association. Conceptually, this required examining two sides of the equation: the relationship between apathy and TMS-derived measures, and the relationship between physical activity and these same neurophysiological parameters. We first focused on the physical activity–TMS side by conducting a systematic review and addressing a key gap in the literature.

6.4. Habitual Physical Activity and Motor Cortex Neurophysiology

We systematically reviewed and synthesized the available evidence on the relationship between habitual physical activity and TMS-derived measures of motor cortex neurophysiology. This was necessary because, although other forms of physical activity such as acute exercise has been shown to transiently influence M1 excitability and inhibition (Singh et al., 2015; El-Sayes et al., 2019; Mellow et al., 2020; Alibazi et al., 2021; Nicolini et al., 2021; Youssef et al., 2024), it remained unclear whether habitual physical activity is associated with neurophysiological parameters of M1. Establishing this relationship was important before examining whether similar neurophysiological measures are also associated with behavioral apathy. This study focused on corticospinal excitability, cortical inhibition, and intracortical facilitation, as these measures reflect distinct aspects of M1 function and are commonly used to probe motor cortical physiology in humans.

The findings showed no reliable association between habitual physical activity and global measures of motor cortical physiology. Specifically, the pooled association between physical

activity and corticospinal excitability was close to zero and statistically equivalent to zero, suggesting that habitual physical activity is unlikely to be meaningfully associated with resting corticospinal output. Similarly, no overall associations were observed for cortical inhibition or intracortical facilitation, and equivalence testing for these inhibitory and facilitatory measures was inconclusive. For intracortical inhibitory and facilitatory measures, the broader confidence interval underscores the need for greater precision before conclusions regarding practical equivalence can be drawn. One factor that may contribute to this uncertainty is that intracortical inhibitory and facilitatory circuits are known to exhibit greater inter-individual variability and may be more sensitive to methodological differences in stimulation parameters and participant characteristics (Orth et al., 2003; Boroojerdi et al., 2000; Maeda et al., 2002). As a result, while the present findings did not provide evidence for meaningful associations between habitual physical activity and intracortical circuitry, they also do not rule out the possibility of small-to-moderate relationships. These findings suggest that the transient neurophysiological effects observed following acute exercise do not translate into stable long-term adaptations in conventional resting TMS-derived measures of motor cortical physiology. While acute exercise may temporarily increase corticospinal excitability and modulate inhibitory circuits through short-lived neurochemical changes, these effects are time-dependent and typically dissipate within minutes (Mellow et al., 2020; Nicolini et al., 2021; Alibazi et al., 2021; Youssef et al., 2024). In contrast, habitual physical activity does not appear to be associated with robust differences in baseline M1 excitability, inhibition, or facilitation, suggesting a dissociation between state-dependent modulation and stable neurophysiological traits.

This study was important in narrowing the potential neurophysiological mechanisms underlying the apathy–physical activity relationship. However, these findings clarified one side of

the proposed neurophysiological pathway by showing that habitual physical activity is not meaningfully associated with measures of M1 neurophysiology. The other side of the equation has been addressed by examining whether behavioral apathy itself is associated with corticospinal excitability and intracortical circuits, independent of physical activity behavior. This step is further supported by evidence that behavioral apathy is associated with alterations in fronto-striatal and motor-related networks, particularly involving the anterior cingulate cortex and SMA, which play a key role in effort sensitivity, action preparation, and the translation of intention into action (Bonnelle et al., 2016; Derosiere et al., 2025). Given the close functional and anatomical coupling between these regions and M1, it remains important to determine whether motor cortical physiology is directly involved in the expression of behavioral apathy.

6.5. Behavioral Apathy and Resting M1 Neurophysiology

After examining whether physical activity was associated with TMS-derived measures of M1 neurophysiology, the final step was to examine the other side of the proposed neurophysiological pathway: whether behavioral apathy itself was associated with M1 corticospinal excitability and intracortical circuits. This was important because, for M1 neurophysiology to represent a plausible mechanism linking apathy and physical activity, behavioral apathy would also need to show meaningful associations with these neurophysiological parameters.

The findings showed that behavioral apathy was not meaningfully associated with CSE, SICI, LICI, or ICF. Importantly, this conclusion was supported not only by non-significant regression coefficients, but also by equivalence testing, which indicated that the associations between behavioral apathy and all four TMS measures were statistically equivalent to zero within predefined negligible-effect bounds. This strengthens the interpretation that the absence of

association was not simply due to insufficient statistical power, but rather that any true associations are likely too small to be practically meaningful in healthy adults.

These findings suggest that behavioral apathy is unlikely to be explained by resting physiological properties of M1. Although behavioral apathy is closely related to reduced self-initiation of action, this does not appear to reflect altered corticospinal excitability or local intracortical inhibitory–facilitatory balance within M1. Instead, the results support the idea that apathy may be more strongly related to higher-order motivational and action-selection systems, including fronto-striatal, cingulate, and supplementary motor networks.

Therefore, studies focusing on neurophysiological parameters helped complete the neurophysiological evaluation of this relationship. The absence of associations between both physical activity and behavioral apathy with M1 measures further weakens the likelihood that conventional resting M1 physiology explains this link. Although the present study did not directly measure other brain systems, the findings align with previous research suggesting that apathy is more strongly related to higher-level networks involved in motivation and action, such as fronto-striatal circuits and interactions between the SMA and M1, which play a key role in effort-based decision-making and action initiation.

This interpretation aligns with the overall pattern observed across the thesis. Behavioral findings showed that apathy is associated with lower physical activity, partly explained by affective attitudes and intentions, whereas neurophysiological results indicated that neither physical activity nor behavioral apathy was meaningfully related to resting TMS-derived measures of M1 function. Together, these findings suggest that the apathy–physical activity relationship is better explained by motivational and affective processes than by baseline motor cortical excitability or intracortical circuits.

Overall, these results indicate that reduced self-initiated behavior in apathy is unlikely to reflect alterations in resting corticospinal excitability or intracortical balance. Rather, it may arise from disruptions in systems governing valuation, effort allocation, and the initiation of action, refining the mechanistic understanding of how apathy contributes to physical inactivity.

6.6. Strengths and Limitations

This thesis has several strengths. First, the use of a behavioral apathy measure is a key strength, as it specifically captures action initiation and goal-directed behavior, which are directly relevant to physical activity engagement. Second, the use of paired-pulse TMS protocols enabled a detailed assessment of intracortical inhibitory and facilitatory processes, providing a comprehensive characterization of M1 neurophysiology. Third, physical activity was assessed using accelerometry, enhancing ecological validity and reducing bias associated with self-report measures. Finally, the relatively large sample size for TMS research ($N = 100$), combined with the integration of behavioral, psychological, and neurophysiological approaches, allowed for a rigorous and comprehensive examination of the apathy–physical activity relationship.

Despite these strengths, some limitations should be acknowledged. First, TMS measures were obtained at rest, which may not capture task-dependent or network-level processes involved in action initiation and effort-based decision-making. Second, the cross-sectional design prevents conclusions about causality and directionality of the relationship between apathy and physical activity. Third, the sample consisted of healthy adults, which may limit generalizability to clinical populations.

6.7. Conclusion

The findings of this thesis suggest that apathy is a meaningful barrier to physical activity, but that this relationship is better explained by motivational and behavioral processes than by

resting measures of M1 neurophysiology. Across the studies, a consistent pattern emerged: higher apathy was associated with lower physical activity, and this association appeared to operate partly through weaker intentions and less positive affective attitudes toward physical activity. In contrast, neither habitual physical activity nor behavioral apathy showed meaningful associations with TMS-derived measures of corticospinal excitability, intracortical inhibition, or intracortical facilitation.

This pattern refines the original framework of the thesis. The initial rationale proposed that apathy may affect physical activity through both behavioral and neurophysiological pathways. The behavioral pathway was supported: individuals with higher behavioral apathy appeared less likely to form strong intentions to be active, partly because they held less favorable affective attitudes toward physical activity. This suggests that apathy may interfere with the valuation of physical activity before action occurs. In other words, the difficulty may not lie in the motor system's capacity to produce movement, but in the motivational processes that determine whether movement is initiated in the first place.

By contrast, the neurophysiological pathway involving resting M1 function was not supported. It showed that habitual physical activity was not reliably associated with resting M1 excitability or intracortical circuits. Similarly, behavioral apathy showed negligible associations with these same TMS measures. Together, these findings suggest that resting TMS measures of M1 function are unlikely to explain why individuals with higher apathy engage in less physical activity. Rather than reflecting altered baseline motor cortical excitability, the apathy–physical activity relationship may arise from processes involved in effort valuation, reward sensitivity, intention formation, and action selection.

These findings do not mean that the motor system is irrelevant to apathy or physical activity. Instead, they suggest that the relevant motor-related mechanisms may not be captured by resting single-pulse or paired-pulse TMS measures of M1. Apathy may involve higher-order motor-motivational circuits, such as interactions between the anterior cingulate cortex, SMA, basal ganglia, and M1. These circuits may be particularly important during task preparation, effort-based decision-making, or action initiation, rather than during resting-state assessment. Therefore, future studies may need to move beyond local M1 excitability and examine dynamic network-level processes, including SMA–M1 connectivity, task-dependent corticospinal modulation, and neural responses during effort-based choices.

Taken together, the findings of this thesis suggest that apathy may contribute to physical inactivity through difficulties in translating motivational value into action. However, this process does not appear to be explained by stable differences in resting M1 corticospinal excitability or intracortical inhibitory and facilitatory circuits. The relationship between apathy and physical activity appears to be driven more strongly by affective attitudes, intentions, and higher-order motivational systems. Future research should therefore investigate dynamic, task-based, and network-level mechanisms that may better capture how apathy disrupts the initiation and maintenance of physically active behavior.

The present findings highlight several directions for future research. First, in the present study, stimulation was delivered using a standard coil orientation targeting conventional M1 excitability measures. However, altering the direction and orientation of the TMS coil may engage different intracortical circuits and neural populations, potentially revealing associations that were not detected with the current protocol. Therefore, future studies may benefit from examining

whether different coil orientations or current directions provide greater sensitivity to motivational or apathy-related neurophysiological differences.

Second, future work should focus on network-level mechanisms rather than isolated regions. Apathy has been consistently linked to fronto-striatal and SMA circuits involved in valuation and action initiation. Techniques such as dual-site TMS, connectivity analyses, or multimodal approaches combining TMS with neuroimaging may help clarify how interactions between these regions contribute to reduced physical activity.

Third, future studies should examine whether these findings generalize to clinical populations and older adults, where apathy is more pronounced and may be associated with greater neural alterations.

Finally, intervention-based research is needed to translate these findings into practice. Studies targeting affective attitudes, intention formation, and perceived effort, such as through behavioral activation, graded activity, or reward-based approaches, may help determine whether modifying motivational processes leads to sustained increases in physical activity in individuals with higher apathy.

6.8. References for General Introduction and Discussion

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7. Publications

(*first co-authorship)

7.1. Preprints (not peer reviewed)

22. **Farajzadeh A**, Harroum N, Boisgontier MP. (2026). Behavioral apathy shows negligible associations with M1 corticospinal excitability and intracortical circuits. *SportRxiv*. <https://doi.org/10.51224/SportRxiv.822>
21. **Farajzadeh A**, Park K, Dumas T, Lahart I.M, Carlsen AN, Boisgontier MP. (2026). Physical activity and motor cortex neurophysiology: a systematic review and meta-analysis of transcranial magnetic stimulation measures of excitability, inhibition, and facilitation. *SportRxiv*. <https://doi.org/10.51224/SportRxiv.815>
20. Jabouille F, **Farajzadeh, A**, Boisgontier MP. (2026). Approach-avoidance tendencies and physical activity level: a systematic review and meta-analysis. *SportRxiv*. <https://doi.org/10.51224/SportRxiv.839>
19. Jabouille F*, **Farajzadeh A***, Guillemot A, Martine J, Sadek N, Klinger L, Iliut C, Kapsa V, Boisgontier MP. (2025). Replicability and transparency in physical therapy research: time to wake up. *MedRxiv*. <https://doi.org/10.1101/2025.09.23.25336497>

7.2. Refereed Articles

18. **Farajzadeh A**, Hebert A, Lahart IM, Bilodeau M, Boisgontier MP. (In press). Apathy and physical activity: a systematic review and meta-analysis. *Physiotherapy Canada*. <https://doi.org/10.3138/ptc-2024-0050>
17. Fessler L, Maltagliati S, Meyer P, Finckh A, Cullati S, Sander D, Friese M, Wiers RW, **Farajzadeh A**, Luthy C and Sarrazin P. (2026). Anatomy of a failure: a retrospective evaluation of a cognitive bias modification intervention to promote physical activity in

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16. **Farajzadeh A**, Jabouille F, Benoit N, Bezeau O, Bourgie T, Gerro B, Ouimet J, Boisgontier MP. (2025). Apathy, intentions, explicit attitudes, and approach-avoidance tendencies in physical activity behavior. *Communications in Kinesiology*, 1(6), 1-20. <https://doi.org/10.51224/cik.2024.68>
 15. Goubran M*, **Farajzadeh A***, Lahart IM, Bilodeau M, Boisgontier MP. (2025). Relationship between fear of movement and physical activity in patients with cardiac, rheumatologic, neurologic, pulmonary, or pain conditions: a systematic review and meta-analysis. *Physical Therapy*, 105(6), pzaf050. <https://doi.org/10.1093/ptj/pzaf050>
 14. Cheval B, Maltagliati S, Saoudi I, Fessler L, **Farajzadeh A**, Sieber S, Cullati S, Boisgontier MP. (2023). Physical activity mediates the effect of education on mental health trajectories in older age. *Journal of Affective Disorders*, 336, 64-73. <https://doi.org/10.1016/j.jad.2023.05.052>
 13. Cheval B, Saoudi I, Maltagliati S, Fessler L, **Farajzadeh A**, Sieber S, Cullati S, Boisgontier MP. (2023). Initial status and change in cognitive function mediate the association between academic education and physical activity in adults over 50 years of age. *Psychology and Aging*, 38(6), 494-507. <https://doi.org/10.1037/pag0000749>
 12. **Farajzadeh A**, Goubran M, Fessler L, Cheval B, Allen Z, Boisgontier MP. (2023). Training older adults to inhibit the automatic attraction to sedentary stimuli: A cognitive-bias-modification protocol. *European Rehabilitation Journal*, 3(1), 1-9. <http://doi.org/10.52057/erj.v3i1.32>

11. **Farajzadeh A**, Goubran M, Beehler A, Cherkaoui N, Morrison P, de Chanaleilles M, Maltagliati S, Cheval B, Miller MW, Sheehy L, Bilodeau M, Orsholits D, Boisgontier MP. (2023). Automatic approach-avoidance tendency toward physical activity, sedentary, and neutral stimuli as a function of age, explicit affective attitude, and intention to be active. *Peer Community Journal*, 3, e21. <https://doi.org/10.24072/pcjournal.246>
10. Ostadzadeh A, Amini M, Hassani Mehraban A, Maroufizadeh S, **Farajzadeh A**. (2023). The effect of occupation-based modified constraint-induced movement therapy on the participation of children with cerebral palsy: a single-blind randomized controlled trial. *Iranian Journal of Child Neurology*, 17 (2), 39-54. <https://doi.org/10.22037/ijcn.v17i2.37654>
9. Cheval B, Maltagliati S, Fessler L, **Farajzadeh A**, Abdallah S, Vogt F, Dubessy M, Lacour M, Miller MW, Sander D, Boisgontier MP. (2022). Physical effort biases the perceived pleasantness of neutral faces: a virtual reality study. *Psychology of Sport & Exercise*, 63, 102287. <https://doi.org/10.1016/j.psychsport.2022.102287>
8. **Farajzadeh A**, Akbarfahimi M, Maroufizadeh S, Miri Lavasani N. (2021). Factor associated with quality of life among caregivers of people with spinal cord injury. *Occupational Therapy International*, 2021, 9921710. <https://doi.org/10.1155/2021/9921710>
7. **Farajzadeh A**, Dehghanizadeh M, Maroufizadeh S, Amini M, Shamili A. Predictors of mental health among parents of children with cerebral palsy during the COVID-19 pandemic in Iran: A web-based cross-sectional study. (2021). *Research in Developmental Disabilities*, 112, 103890. <https://doi.org/10.1016/j.ridd.2021.103890>
6. Shamili A, Mehraban AH, Azad A, Raissi GR, Shati M, **Farajzadeh A**. (2021). Effectiveness of self-action observation therapy as a novel method on paretic upper limb and cortical

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5. Jamali A, Karimpour M, Saneii SH, **Farajzadeh A**, Amini M. (2020). Factor affecting the caregiver difficulties in caring of children with cerebral palsy. *Function and Disability Journal*, 3, 1-10. <https://doi.org/10.32598/fdj.3.66.1>
 4. **Farajzadeh A**, Maroufizadeh S, Amini M. (2019). Factor associated with quality of life among mothers of children with cerebral palsy. *International Journal of Nursing Practice*, 26(3), e12811. <https://doi.org/10.1111/ijn.12811>
 3. **Farajzadeh A**, Akbarfahimi M, Maroufizadeh S, Rostami HR, Kohan AH. (2018). Psychometric properties of Persian version of the Caregiver Burden Scale in Iranian caregivers of patients with spinal cord injury. *Disability and Rehabilitation*, 40(3), 367-372. <https://doi.org/10.1080/09638288.2016.1258738>
 2. **Farajzadeh A**, Amini M, Maroufizadeh S, Wijesinghe CJ. (2018). Caregiver Difficulties Scale (CDS): translation and psychometric evaluation among iranian mothers of cerebral palsy children. *Occupational Therapy in Health Care*, 32(1), 28-43. <https://doi.org/10.1080/07380577.2017.1422607>
 1. **Farajzadeh A**, Akbarfahimi M, Nedjat S, Kohan A, Saberi H. (2015). Translation and validation of a caregiver burden scale (CBS) among caregivers of patients with spinal cord injury. *Scientific Journal of Rehabilitation Medicine*, 5(1), 1-12.

8. Appendices

Appendix A. Lille Apathy Rating Scale (LARS-e)

Action Initiation Subscale (Behavioral Apathy)

Below are a number of statements. Each statement asks you to think about your life over the **last 2 weeks**.

For each statement, circle a number from **1 to 5** to indicate how true the statement is of you over the last 2 weeks (i.e., how appropriately it describes your life right now).

- Select “**1**” if the statement does not describe you at all
- Select “**5**” if the statement describes you perfectly
- Select numbers in between accordingly
- Select “**NA**” if the statement is not applicable to you

Response Scale

- **1** = Completely **UNTRUE** (exactly the opposite of me)
 - **2** = Mostly untrue of me
 - **3** = Neither untrue nor true of me
 - **4** = Mostly true of me
 - **5** = Completely **TRUE** (exactly describes me)
-

In the last 2 weeks...

1. I didn't like to laze around.
Response (1–5 or NA): _____
2. I liked to have a busy schedule.
Response (1–5 or NA): _____
3. I usually got up in the morning even if I didn't have to go to work.
Response (1–5 or NA): _____
4. I got things done when they needed to be done, without being reminded by others.
Response (1–5 or NA): _____
5. I made decisions firmly and without hesitation.
Response (1–5 or NA): _____
6. When I had something I needed to do, I did it straightaway so it was out of the way.
Response (1–5 or NA): _____

7. I liked being in charge.

Response (1–5 or NA): _____

8. I didn't achieve my goals for the day; I got annoyed.

Response (1–5 or NA): _____

9. If I had to RSVP to an invitation, I did it promptly, without needing a reminder.

Response (1–5 or NA): _____

10. I was easily able to decide to do things by myself, without needing someone to push or encourage me.

Response (1–5 or NA): _____

11. Getting something done by 9 a.m. gave me a sense of satisfaction.

Response (1–5 or NA): _____

Appendix B. International Physical Activity Questionnaire (IPAQ)

(Craig et al., 2003)

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise, or sport.

Moderate to Vigorous Physical Activity

Vigorous Physical Activity

Think about all the **vigorous activities** that you did in the **last 7 days**. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least **10 minutes at a time**.

During the **last 7 days**, on how many days did you do **vigorous physical activities** such as heavy lifting, digging, aerobics, or fast bicycling?

- **Number of days per week:** _____
- **Number of minutes per day:** _____

Moderate Physical Activity

Think about all the **moderate activities** that you did in the **last 7 days**. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least **10 minutes at a time**.

During the **last 7 days**, on how many days did you do **moderate physical activities** such as carrying light loads, bicycling at a regular pace, or doubles tennis? **Do not include walking.**

- **Number of days per week:** _____
- **Number of minutes per day:** _____

Sedentary Behavior

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing coursework, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down while watching television.

During the **last 7 days**, how much time did you spend **sitting**?

- **Number of days per week:** _____
- **Number of minutes per day:** _____

Appendix C. Depression Subscale of the Depression Anxiety Stress Scales (DASS-42)

The **Depression subscale** of the *Depression Anxiety Stress Scales (DASS-42)* consists of 14 items designed to assess depressive symptoms. Participants are asked to rate the extent to which each statement applied to them over the past week using a 4-point Likert scale:

- **0:** Did not apply to me at all
- **1:** Applied to me to some degree, or some of the time
- **2:** Applied to me to a considerable degree, or a good part of the time
- **3:** Applied to me very much, or most of the time

I couldn't seem to experience any positive feeling at all.

(0–3): _____

I found it difficult to work up the initiative to do things.

(0–3): _____

I felt that I had nothing to look forward to.

(0–3): _____

I felt down-hearted and blue.

(0–3): _____

I was unable to become enthusiastic about anything.

(0–3): _____

I felt I wasn't worth much as a person.

(0–3): _____

I felt that life was meaningless.

(0–3): _____

I found myself getting agitated.

(0–3): _____

I felt that I had lost interest in just about everything.

(0–3): _____

I felt I wasn't enjoying anything anymore.

(0–3): _____

I felt like I was pretty worthless.

(0–3): _____

I felt I was close to panic.

(0–3): _____

I felt that I had nothing to offer the world.

(0–3): _____

I felt overwhelmed by the things I had to do.

(0–3): _____

Appendix D

Descriptive statistics after additional filtering (Sensitivity analysis)

For the TMS measures, the mean values were 0.61 ± 0.41 mV for CSE, 0.329 ± 0.210 for SICI, 0.144 ± 0.203 for LICI, and 1.46 ± 0.60 for ICF (Fig. 1). Because missing data were handled using listwise deletion within each model, the analytic sample size varied slightly across regression analyses, ranging from $n = 88$ for LICI to $n = 97$ for CSE, with $n = 91$ for SICI and $n = 91$ for ICF.

Regression table after additional filtering (Sensitivity analysis)

Adjusted associations of corticospinal excitability (CSE), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and intracortical facilitation (ICF) with behavioral apathy.

Variable	CSE (n = 97)			SICI (n = 92)			LICI (n = 90)			ICF (n = 91)		
	b	95CI	p	b	95CI	p	b	95CI	p	b	95CI	p
(Intercept)	1.58	1.33 ;1.84	<.001 ***	1.67	1.41 ;1.93	<.001 ***	1.68	1.41 ;1.94	<.001 ***	1.69	1.42 ;1.95	<.001 ***
Age	0.065	-0.08 ;0.21	.359	0.10	-0.05 ;0.24	.185	0.11	-0.04 ;0.25	.141	0.12	-0.03 ;0.26	.114
Gender	-0.05	-0.29 ;0.20	.704	-0.14	-0.40 ;0.11	.261	-0.14	-0.41 ;0.11	.267	-0.16	-0.42 ;0.10	.226
Data source	-0.12	-0.41 ;0.16	.404	-0.18	-0.47 ;0.11	.226	-0.19	-0.48 ;0.10	.197	-0.19	-0.47 ;0.10	.190
DASS	0.15	0.04-0.27	.011 *	0.16	0.03 ;0.28	.012 *	0.16	0.04 ;0.28	.012 *	0.16	0.03 ;0.28	.013 *
CSE	0.007	-0.11 ;0.13	.902									
SICI				-0.06	-0.18 ;0.06	.543						
LICI							-0.07	-0.20 ;0.05	.256			
ICF										-0.05	-0.19 ;0.08	.389
R ²		.085			.120			.128			.114	
Adjusted R ²		.035			.068			.075			.062	
F, Model p		1.69, p = .145			2.32, p = .058			2.42, p = .042			2.23, p = .058	

Note. * $p < .05$, *** $p < .001$, b = unstandardized regression coefficient, 95CI = 95% confidence interval, DASS = Depression subscale of the Depression Anxiety Stress Scale, R² = coefficient of determination, adjusted R² = coefficient of determination adjusted for the number of predictors in the model, F = overall model test statistic.

Equivalence testing after additional filtering (Sensitivity analysis)

Equivalence testing after additional filtering showed that the effects of all TMS measures fell within the negligible-effect interval of -0.2 to 0.2 apathy-score units per 1-standard-deviation increase in the predictor. Specifically, the 90% confidence intervals were $[-0.09, 0.11]$ for CSE, $[-0.16, 0.04]$ for SICI, $[-0.18, 0.03]$ for LICI, and $[-0.17, 0.05]$ for ICF. Corresponding two one-sided test (TOST) p-values were .001, .016, .026, and .019 for CSE, SICI, LICI, and ICF respectively, indicating statistical equivalence for all four TMS measures. Overall, these findings indicate that the adjusted associations of M1 corticospinal excitability, intracortical inhibition, and facilitation with behavioral apathy were sufficiently small to be considered negligible.